IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC, Plaintiffs, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 06-286-GMS **REDACTED – PUBLIC VERSION**

BARR LABORATORIES, INC.'S MOTION *IN LIMINE* TO EXCLUDE ANY DOCUMENTS RELATED TO BARR'S ANDA TO SHOW PROOF OF COPYING

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PRELIMINARY STATEMENT

This Court should exclude evidence regarding Barr's ANDA and the development of Barr's ANDA product to establish "copying" as part of Plaintiffs' case on secondary considerations of nonobviousness. The undisputed factual testimony conclusively establishes that did not "copy" the patented invention within the meaning of the patent law. Rather,

Accordingly, the development of Barr's ANDA product is wholly immaterial to Plaintiffs' copying allegations and should be excluded.

ARGUMENT

Under Section 103 of the Patent Act, an invention is unpatentable if it would have been obvious to a person of ordinary skill in the art. 35 U.S.C. § 103(a). Obviousness is a question of law that depends on several factual inquires. *Richardson- Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). One such factual inquiry involves secondary considerations of non-obviousness, including whether the alleged infringer directly copied the patented invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000). The deliberate copying of the patented invention may be evidence that the invention is non-obvious if there is some "nexus between [the] copying and the nonobviousness of the claimed invention." *Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1028 (Fed. Cir. 1985), *overruled on other grounds by Midwest Industries, Inc. v. Karavan Trailers, Inc.*,175 F.3d 1356 (Fed. Cir. 1999). For example, copying is particularly relevant "where the copyist had itself attempted for a substantial length of time to design a similar device, and had failed." *Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1196 (Fed. Cir.

2003) (citation omitted). Evidence of copying in ANDA cases, however, is largely irrelevant to nonobviousness because the ANDA process effectively requires an ANDA applicant to copy the brand drug referenced in its ANDA. *See Aventis Pharma v. Lupin LTD*, No. 2:05cv421, 2006 U.S. Dist. LEXIS 48246 at *138 (E.D. Va. July 17, 2006), *rev'd on other grounds*, 499 F.3d 1293 (Fed. Cir. 2007) (attached as Exhibit 1); *Aventis Pharma Deutschland GMBH., v. Lupin LTD*, 403 F. Supp. 2d 484, 486 (E.D. Va. 2005); *Eli Lilly & Co. v. Teva Pharms., Inc.*, No. IP 02-0512-C-B/S, 2004 U.S. Dist. LEXIS 14724 at *117, n.21 (S.D. Ind. July 29, 2004) (attached as Exhibit 2).[1] Thus, an ANDA applicant's "copying" of the branded drug is not competent evidence of deliberate copying of the patented invention. Simply put, the motivation for the "copying" exists not because of the patented invention but because of regulatory requirements.

The Hatch-Waxman Act requires ANDA applicants to demonstrate bioequivalence to the branded product to gain approval of their ANDA. 21 U.S.C. 355(j)(2)(A)(iv). Because determining bioequivalence for topically-acting products such as nasal sprays is particularly difficult, the FDA has promulgated a draft guidance document that informs generic manufacturers that nasal sprays should be qualitatively the same and quantitatively essentially the same in formulation to the branded drug. This means the ANDA product should contain both the same active ingredient and the same inactive ingredients in essentially the same amounts as the branded drug. (*See* Ex. 3, 2003 FDA Draft Guidance Document at 5 (FDA "relies on qualitative and quantitative sameness of formulation[s]" to determine bioequivalence); *id.* at 8 ("For product equivalency, we recommend that . . . the inactive ingredients in the test product

[1] The circumstances in which copying might be relevant in an ANDA case—which are not present here—are those in which the generic manufacturers already have the product on the market in a different formulation. *See, e.g., Forest Labs, Inc. v. Ivax Pharms., Inc.*, 438 F. Supp.2d 479, 469 (D. Del 2006) (finding copying relevant to obviousness where several generic companies already in the market sought approval for new formulation).

formulation be qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the inactive ingredients in the formulation of the reference listed drug."); Ex. 4, 1999 FDA Draft Guidance Document at 7 (same)).[2]

Thus, in cases involving ANDAs filed by generic drug companies, especially when topically-active nasal sprays are involved, the generic will almost always copy the branded drug because "that is what generic drug companies do." *Aventis Pharma*, 2006 U.S. Dist. LEXIS 48246 at *138. For these reasons, Courts have strictly limited the use of ANDAs as evidence of copying. *See, e.g.,*. *Eli Lilly & Co.*, 2004 U.S. Dist. LEXIS 14724 at *117 n.21 (ruling that since "the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, [a defendant's] demonstration of equivalency to [the drug] to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention"); *Aventis Pharma*, 2006 U.S. Dist. LEXIS 48246 at *138.

Here, Plaintiffs intend to rely upon

as evidence of copying. (*See* Ex. 5 at 74-76).

[2] FDA's "sameness" recommendations for inactive ingredients in nasal sprays are more stringent than FDA requirements for systemically distributed drugs, such as most tablets and capsules, which need not contain the same inactive ingredients to obtain FDA approval. *See* 21 C.F.R. § 314.94(a)(9)(ii).

(Ex. 6, Zeevi Tr., p. 63:4-10).

While Plaintiffs have suggested that the FDA guidance on nasal spray bioequivalence is only a recommendation and need not be followed,

This testimony is the only factual evidence in this case regarding Perrigo's or Barr's reasons for allegedly "copying" the branded drug; and it stands uncontradicted. Accordingly, Plaintiffs cannot show any nexus between Barr's copying and the alleged non-obviousness of its product. *Eli Lilly & Co.*, 2004 U.S. Dist. LEXIS 14724 at *117 n.21 ("[A defendant's] demonstration of equivalency to [the drug] to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention"). Allowing Plaintiffs to introduce evidence of Barr's or Perrigo's copying as evidence of non-obviousness would require additional factual witnesses, which would unnecessarily lengthen the trial to address these irrelevant matters.

CONCLUSION

For the foregoing reasons, Barr respectfully requests that the Court enter an order precluding Plaintiffs from offering any evidence related to the development of Barr's ANDA product to show evidence of copying.

DATED: March 20, 2008

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on April 14, 2008, I caused to be electronically filed a true and correct copy of the foregoing redacted document, ***Barr Laboratories Inc.'s Motion in Limine to Exclude Any Documents Related to Barr's ANDA to Show Proof of Copying***, with the Clerk of the Court using CM/ECF, which will send notification of such filing to the following counsel of record:

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I further certify that on April 14, 2008, I caused a copy of the foregoing redacted document to be served by e-mail and hand delivery on the above-listed counsel and on the following non-registered participants in the manner indicated:

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ORDER

Barr Laboratories, Inc. having moved *in limine* to exclude evidence relating to Barr's ANDA or to the development of Barr's ANDA product to prove copying, and the Court having considered the parties' submissions thereon,

IT IS HEREBY ORDERED this ____ day of _____2008, that Barr's Motion is hereby GRANTED.

_____
Honorable Gregory M. Sleet, U.S.D.J.

EXHIBIT 1

LEXSEE 2006 U.S. DIST. LEXIS 48246

AVENTIS PHARMA DEUTSCHLAND GMBH and KING PHARMACEUTICALS, INC., Plaintiffs v. LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants.

Civil Action No. 2:05cv421

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF VIRGINIA, NORFOLK DIVISION

2006 U.S. Dist. LEXIS 48246

July 17, 2006, Decided
July 17, 2006, Filed

SUBSEQUENT HISTORY: Reversed by Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 2007 U.S. App. LEXIS 21753 (Fed. Cir., Sept. 11, 2007)

PRIOR HISTORY: Aventis Pharma Deutschland GMBH v. Lupin Ltd., 2006 U.S. Dist. LEXIS 36277 (E.D. Va., June 5, 2006)

COUNSEL: [*1] For Aventis Pharma Deutschland GmbH, Plaintiff: Alan Dale Albert, Christopher David Lagow, Ray Webb King, LeClair Ryan PC, Norfolk, VA; Benjamin Chia-Ho Hsing, Catherine Youssef, Joel Katcoff, Sapna Walter Palla, Steven James Glassman, Kaye Scholer LLP, New York, NY; Dana Johannes Finberg, LeClair Ryan PC, Richmond, VA; Douglas Allen Tucker, Kaye Scholer LLP, Washington, DC.

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For Lupin Ltd., Lupin Pharmaceuticals, Inc., Defendants: Adam Glenn Kelly, Alice L Riechers, Deanne M Mazzochi, Paul J Molino, William A Rakoczy, Rakoczy Molino Mazzochi Siwik LLP, Chicago, IL; Conrad Moss Shumadine, Willcox & Savage PC, Norfolk, VA.

For Lupin Ltd., Counter Claimant: Conrad Moss Shumadine, Willcox & Savage PC, Norfolk, VA.

For Aventis Pharma Deutschland GmbH, Counter Defendant: Alan Dale Albert, LeClair Ryan PC, Norfolk, VA; [*2] Dana Johannes Finberg, LeClair Ryan PC, Richmond, VA.

For King Pharmaceuticals, Inc., Counter Defendant: Alan Dale Albert, LeClair Ryan PC, Norfolk, VA; Dana Johannes Finberg, LeClair Ryan PC, Richmond, VA; Gregory Andrew Castanias, Jones Day, Washington, DC.

JUDGES: Robert G. Doumar, UNITED STATES DISTRICT JUDGE.

OPINION BY: Robert G. Doumar

OPINION

MEMORANDUM OPINION AND ORDER

This case involves an action for patent infringement and counterclaims of invalidity with respect to Altace, the marketing name of a pharmaceutical compound known as Ramipril "substantially free of other isomers." Altace is protected by U.S. Patent No. 5,061,722 (the '722 patent), which was issued on October 29, 1991 and will expire on October 19, 2008. Interestingly enough, the '722 patent is a subsequent patent to a patent known as the '258 patent, which was approved by the Food and Drug Administration ("FDA") for the original marketing and

production of Altace.

On June 5, 2006, this Court issued summary judgment finding infringement based on the doctrine of equivalents. Accordingly, only the defendants' defenses to infringement remain. After a bench trial and for the reasons stated herein, the Court [*3] **FINDS** that the '722 patent is valid and that Lupin's defenses to infringement fail. The Court reaches this decision reluctantly. If the standard applied to Lupin's defenses that the '722 patent was invalid had been by a preponderance of the evidence instead of clear and convincing evidence, the Court might have determined this case in Lupin's favor. Unfortunately for Lupin, however, the standard is clear and convincing evidence, and it was unable to meet this heavy burden.

The Court is also of the view that it lacked the tools necessary to address what it perceives as the most problematic issue in this case, namely that Aventis/King has been able to effectively extend its patent protection for Altace by means of either clever maneuverings or fortuitous happenstance before the Patent and Trademark Office ("PTO") and the FDA. The Court details this in the Findings of Fact infra, but the short version is as follows.

Aventis, by means of a patent (the "'258 patent") that it licensed from the Schering Corporation, obtained FDA approval to market Ramipril using the trade name Altace. It also obtained an extension of the '258 patent from the PTO. The '258 patent has expired, and [*4] Lupin believes it should be able to gain FDA approval to market a generic version of Altace for this reason. The '722 patent, however, now stands in Lupin's way. Aventis obtained the '722 patent after the '258 patent issued and strenuously maintains that it -- not the '258 patent -- discloses Ramipril substantially free of other isomers (or Altace). According to Aventis, this is the "active ingredient" in Altace. In other words, when it suited Aventis' needs, it relied on the '258 patent to gain FDA approval for Altace and requested an extension of the '258 patent before the PTO. Now that the '258 patent has expired, however, it relies on the '722 patent to prevent generic competition. While this concerns the Court, this is not to say that Aventis necessarily acted inequitably; rather, the timeline of patent approvals now works in Aventis' favor. Ultimately, the means of attacking the validity of a patent - anticipation, obviousness, inequitable conduct, enablement, etc. - do not adequately address such a circumstance because the conduct in question is not before the Patent Office but is before the FDA. Considering that the validity of a patent may only be challenged under the [*5] clear and convincing standard, the Court thus reluctantly finds for Aventis/King.

I. Overview

A. The Parties

Aventis Pharma Deutschland GMBH ("Aventis") is the current holder of the '722 patent [1]; King Pharmaceuticals ("King") is the exclusive licensee of the '722 patent, marketing Ramipril under the trade name Altace. Aventis and King are the plaintiffs in this case (collectively referred to as "Aventis/King"). Lupin Ltd., a generic drug company, and Lupin Pharmaceuticals, Inc. are the defendants (collectively referred to as "Lupin").

1 As explained infra, Aventis also was the exclusive licensee of the '258 patent.

B. Procedural History

This action arose on July 19, 2005 when Aventis/King brought a two-count suit against Lupin for patent infringement and inducement of infringement with respect to the '722 patent. Prior to this time, on March 18, 2005, Lupin submitted an "Abbreviated New Drug Application" ("ANDA") with "Paragraph IV certification" to the FDA seeking approval to [*6] market generic versions of Ramipril capsules. [2] Pursuant to 35 U.S.C. § 271(e)(2)(A), this filing allowed Aventis/King to bring "a legal action for patent infringement before the generic drug maker has begun marketing [the drug]." SmithKline Beecham Corp. v. Geneva Pharms., Inc., 287 F. Supp. 2d 576, 582 (E.D. Penn. 2002). If the original patent owner brings suit, as Aventis did here, "then [FDA] approval may not be made effective until the court rules that the patent is not infringed or until the expiration of (in general) 30 months, which ever first occurs." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 677-78, 110 S. Ct. 2683, 110 L. Ed. 2d 605 (1990).

2 This Court explained the ANDA process in more detail in Aventis Pharma Deutschland GMBH v. Lupin Ltd., 403 F. Supp. 2d 484, 486 (E.D. Va. 2005).

The '722 patent at issue has five claims. The parties agreed that only claim 1 required construction. Claim 1 reads in its entirety as follows, with the portions of the [*7] claim requiring construction bolded:

> A **compound** of the formula
>
> [See formula in print version]
>
> or a physiologically acceptable salt thereof, wherein R2 is hydrogen, methyl, ethyl, or benzyl, and wherein hydrogen atoms on the ring carbon atoms in the 1- and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3-position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration, **said compound or salt being substantially free of other isomers.**

'722 patent.

On May 5, 2006, this Court held a Markman Hearing. On May 11, 2006, this Court entered a claim construction order construing the terms "a compound" and "said compound or salt being substantially free of other isomers" found in claim 1 of the '722 patent. See Claim Construction Order Dated May 11, 2006 (Doc. 93). It found that "a compound" is "a fairly broad term meaning a chemically distinct substance formed by union of two or more ingredients (as elements) in definite proportion by weight and definite structural arrangement. [*8] " Id. at 1. It also found that "said compound or salt being substantially free of other isomers" means that "[R]amipril, the 'said compound,' is largely but not necessarily free of other isomers. In other words, 'substantially free of other isomers' qualifies the compound by indicating that it may not be 100% pure or 100% free of other isomers." Id. at 2.

On June 5, 2006, based on the doctrine of equivalents, this Court granted Aventis/King's motion for summary judgment on infringement subject to the condition that the '722 patent is found valid. Given this decision, Aventis/King's primary task in this case became to rebut Lupin's various defenses to infringement. Lupin first attacked the validity of the '722 patent, arguing anticipation under 35 U.S.C. § 102(a), (b), (e) and/or (g); obviousness under 35 U.S.C. § 103; enablement under 35 U.S.C. § 112, P1; and lack of written description under 35 U.S.C. § 112 P1. In addition, Lupin maintained that the '722 patent was unenforceable due to Aventis' alleged inequitable conduct before the PTO. Finally, Lupin asserted the defenses of equitable [*9] estoppel and prosecution laches.

On June 6, 2006, this Court held a bench trial. On June 14, 2006, at the conclusion of Lupin's case, the Court granted Aventis/King's motion for judgment as a matter of law with respect to Lupin's inequitable conduct defense. The Court overruled the motion with respect to obviousness and reserved ruling with respect to anticipation, enablement, and prosecution laches. On June 20, 2006, the Court granted Aventis/King's motion for judgment as a matter of law with respect to prosecution laches.

On June 26, 2006, the parties submitted post-trial briefs. The parties submitted their replies on July 3, 2006. The Court heard closing arguments on July 13, 2006. Pursuant to Rule 52(a) of the Federal Rules of Civil Procedure, the Court now states its findings of fact and conclusions of law. The Court will emphasize its findings that it concludes are particularly relevant to this case.

II. Findings of Fact

A. Background: Chemistry Concepts Relevant to this Case

1. A Person of Ordinary Skill in the Art

In this case, the level of ordinary skill in the art is high. The Court **FINDS** that a person [*10] of ordinary skill in the art would be someone with a Ph.D. in chemistry or organic chemistry with knowledge of stereochemistry or have a similar amount of training in association with preparing chemical compounds in the pharmaceutical industry and stereochemistry. Such a person would be familiar with methods for preparing, isolating, and characterizing pharmaceutical compounds and have knowledge of stereochemistry.

2. Stereochemistry

Stereochemistry is a subfield of chemistry that is concerned with how molecules are oriented in

three-dimensional space. Isomers or "stereoisomers" are important concepts in stereochemistry. A stereoisomer is a term that refers to chemical compounds that have the same constituent atoms but are arranged in a unique pattern. Stereoisomers, in other words, are molecules that have the same building blocks but differ in their spatial arrangement. [3]

> 3 Stereoisomers are not constitutional isomers, which are isomers having the same molecular formula but their atoms are connected up in a different pattern. Ganem at 59: 24-25.

[*11] Enantiomers are a pair of stereoisomers that are non-superimposable mirror images of each other. They are like left and right hands: facing each other, they each look like a reflection of the other, but placing one on top of the other reveals that their spatial orientations are different. Mosberg at 21: 14-18; Ganem at 175: 6-7. A racemate, or racemic mixture, has an equal mixture of two enantiomers. Mosberg at 23: 15-16. Diastereomers are stereoisomers that are not enantiomers. They are more different from each other than enantiomers are different from each other. In fact, unlike enantiomers, diastereomers usually have different melting and boiling points. Ganem at 174: 13-25.

In stereochemistry, a stereocenter generally refers to a carbon atom that has four different types of atoms or groups of atoms attached to it. This type of stereocenter is known as a chiral carbon. Ganem at 173: 13-18. Chiral carbons can exist in two possible three-dimensional configurations, known as the "R-configuration" and the "S-configuration" pursuant to a set of rules known as the Cahn-Ingold-Prelog system. Ganem at 171-72: 25, 2-4. The Cahn-Ingold-Prelog system, which a person of ordinary skill in [*12] the art would know, allows a chemist to understand a compound's three-dimensional shape simply by looking at how the structure is drawn on a piece of paper. The terms "S" and "R" are ways in which chemists describe a right-hand or left-hand version of a compound.

3. Compound Definitions and Structures

Because the parties compare the structures of Captopril, Enalapril, and Ramipril, three ACE-inhibiting compounds that reduce high blood pressure, see infra, a review of how the parties refer to and define portions of the compounds is necessary. A bicyclic compound is a compound that contains two rings that share atoms with each other. The shared atoms constitute a "bridge." "Bridgehead carbons," more specifically, are the carbon atoms at which the two rings meet in a bicyclic compound. Ramipril has a bicyclic ring that consists of two five-membered rings fused together. [4] The parties refer to this ring as a "5,5 bicyclic." [5] The parties refer to where the rings meet as the "bridgehead." The parties refer to the chain of compounds to which the "5,5" bicyclic is attached as the "side chain." The following depiction illustrates these concepts:

[See formula in print version]

As [*13] the illustration demonstrates, the Ramipril molecule may be characterized as having two parts: 1) the bicyclic ring which contains the bridgehead atoms, and 2) the side chain, which is attached to the bicyclic ring.

> 4 At times, the parties also refer to ring as the "proline ring." An amino acid that has a five-membered ring is called a proline.
>
> 5 A "6, 5 bicyclic is where one ring has six sides (atoms) and the other, connecting ring has five sides (atoms)." Ganem at 399: 14-16.

When groups or atoms lie on the same side of a plane in a molecule, they are referred to as *"cis."* When groups or atoms lie on opposite sides of plane in a molecule, they are referred to as *"trans."* The terms *"endo"* (or "syn") and *"exo"* in a bicyclic ring system describe the relative orientation of groups attached to non-bridgehead carbons. A substituent -- an atom or group of atoms -- attached to a ring is endo (*syn*) if it is oriented toward the other ring, making a bowl or "V" shape. It is *exo* if the substituent [*14] is oriented away from it, giving it a flatter shape. Mosberg at 47: 3-4. In Ramipril, the bicyclic ring is known as *"cis, endo"* because all three chiral centers on the are in the S-configuration and because the ring is oriented in a certain way.

4. Relevant Separation Techniques

Throughout this case, the parties refer to several separation techniques used by chemists. Fractional crystallization is a method of separating substances based on differences in their solubility. If two or more substances are dissolved in a solvent, they will crystallize out of solution at different rates. Ganem at 61: 1-22. Chromatography generally is a method of passing a mixture through a solid substance. Thin layer

chromatography (TLC) involves passing a solution through a thin layer of absorbent material. Column chromatography involves passing a substance through a glass column (or tube) that is packed with some kind of filter. A chemical sample is placed on top of the column. Some kind of solvent is then poured into the top over the chemical sample. Gravity draws the solvent downwards, and different compounds or components of the mixture travel through the solid at different rates and are [*15] separated. The separated compounds are collected in test tubes placed below the glass column. These are standard techniques used to separate compounds. They are also the standard methods used to separate diastereomers, because diastereomers usually have different chemical properties and separate well using these methods.

Enantiomers -- stereoisomers that are mirror images of each other -- require a different separation technique because they are so similar. Ganem at 174: 13-25. The best way to separate a mixture of enantiomers is to use other enantiomers. Ganem at 175: 6-8. In essence, this is done by placing a material that is chemically either in the all (R) or all (S) configuration in the column chromatography apparatus. If a solvent containing the opposite configuration is poured through the material, one of the enantiomers will be drawn through the material faster than the other and thus separate. Ganem at 176: 8-22. The same kind of process may be used by means of crystallization techniques.

Other separation methods include spectroscopy, which identifies substances by means of the spectrum emitted or absorbed, and nuclear magnetic resonance ("NMR"), a type of spectroscopy that [*16] utilizes the magnetic property of an atom's nucleus. Laird at 475: 24.

The Court **FINDS** that a person of ordinary skill in the art in 1981 would have known about all of these methods.

5. Mercuric acetate oxidation

In addition to general separation techniques, of particular importance in this case is a synthetic method of creating compounds called mercuric acetate oxidation. Aventis contests its operability in relation to Example 20 found in the "Schering References," references for which Lupin claims constitute the prior art in this case. Dr. Laird, Lupin's expert in synthetic chemistry, explained the mercuric acetate oxidation process. The Court found him highly credible and notes that, even though he was an expert witness for Lupin, he is also currently serving as a consultant for Aventis and has served as an expert witness for Aventis in the past. Laird at 440: 2-24.

Example 20 begins with the compound octahydrocyclopentapyrrole, which is to be oxidized by means of mercuric acetate oxidation in the first step of the Example. Laird at 468: 14-15; 468: 16. Mercuric acetate oxidation uses mercuric acetate to produce a chemical transformation known as an "oxidation reaction. [*17] " In the most general sense, what happens in mercuric acetate oxidation is that the oxidizing agent removes the hydrogen from the carbon atom, which produces an iminium salt. Two hydrogen atoms are then removed. Laird at 446: 19-21, 25. This, in short, is the dehydrogenation or oxidation process found in the mercuric acetate oxidation step of Example 20.

Specifically, mercuric acetate is used for the dehydrogenation -- the removal of hydrogen atoms -- of amines. Laird at 449: 12. Amines are compounds that contain nitrogen as the key atom. Laird at 443: 22-25. As explained by Dr. Laird, who used ammonia as an example, primary amines occur when one of three hydrogen atoms in ammonia is replaced by an organic substituent. Laird at 443-44: 24-2. Secondary amines have two organic substituents bound to the nitrogen atom and only one hydrogen. In tertiary amines, organic substituents replace all three hydrogen atoms. Id.

In the context of Example 20, the key step of mercuric acetate oxidation is the conversion of the amine to an imine. Laird at 445: 5-8. An imine is a chemical compound that contains a carbon-nitrogen double bond. Laird at 444: 10-16. Thus the conversion from an amine [*18] to an imine is essentially a conversion from a single to a double bond. Laird at 444: 18. The key contention between Aventis and Lupin is whether the mercuric acetate oxidation process results in giving the second compound in Example 20 a particular imine. Laird at 470: 9-11.

The procedure for the mercuric acetate oxidation process was first described by Professor Nelson Leonard in a well-known scientific paper published on January 20, 1955. Laird at 449: 10-22; Def.'s Ex. 380. He wrote a series of papers subsequent to this publication about the reaction. Laird at 452: 12-17; see, e.g., Def.'s Ex. 348. Leonard's papers focused on tertiary amines. Laird at 466: 17-18. In the Journal of the Chemical Society in 1959, Professor Bonnett published a paper taking

Leonard's oxidation process and applying it to secondary amines. Laird at 466: 13-23; Def.'s Ex. 352. The Court **FINDS** that a person of ordinary skill in the art as of 1981 would have either been aware of these papers on mercuric acetate oxidation or would have known how to access the papers by means of a literature search of the chemical abstracts. See Laird at 451: 1-8.

The Court also **FINDS** that Dr. Leonard's [*19] papers provided a specific procedure with how to carry out the mercuric oxidation process. In general, the procedure for this process involves mixing mercuric acetate with solvent and heating it to "reflux" (boiling). Laird at 456: 11-20. A solid precipitate is then formed, which is a good sign, although not a conclusive one, that oxidation has occurred. Laird at 457: 15-19. The precipitate, which is often white, is then separated, with liquid mercury often coming out as a by-product and which must be filtered off. Laird at 457: 22; 458: 3-4. The product that is left is referred to generally as filtrate, and, in this process, is a yellow liquid. Laird at 458: 10, 14. Pursuant to Leonard's instructions, the white precipitate should then be weighed in order to assess how much oxidation has actually occurred. Laird at 458: 20-25. In the 1950s and 1960s, it was a good way to follow the progress of the oxidation. By the 1980s, other methods such as chromatography and spectroscopic methods could be used to follow how the reaction progressed. Laird at 459: 2-6.

The next step in Leonard's procedure is to add hydrogen sulfide to remove whatever mercuric acetate is left. Laird at 459: 12-14. The [*20] result is a yellow solution and a black precipitate of mercuric sulfide, which, according to Leonard, must be filtered off. Laird at 459: 14-17; 450: 3-6, 15-18. The liquid left should not have any mercury in it after this filtering. At this point, the imine is still in the yellow liquid, and the liquid contains organic compounds, the amine starting material, and any by-products that have occurred. Laird at 459: 11-13, 21. Thus another separation step is required. In the 1980s, the standard techniques for isolating an organic compound from the remaining liquid included adding an organic solvent to distill the product, a crystallization process, or chromatography. Laird at 461: 1-8.

With respect to adding an organic solvent, Dr. Laird explained that the extraction occurs by adjusting the acidity or basisity (adjusting the pH) of the aqueous (water) layer. Laird at 460: 24-25; 461: 1-2. According to Dr. Laird, Professor Leonard's paper explains that, by adding base to the yellow liquid, the desired product is released. Laird at 462: 23-24. The result is the product dissolved in organic solvent. Leonard's paper also explains that a chemist knows he has the correct product by evaporating [*21] the organic solvent and distilling it carefully. Laird at 463: 9-16. The remaining solid or liquid is then generally analyzed by spectroscopy. Laird at 463: 23-24.

Because mercuric acetate is toxic, an alternative method using a different reagent that achieves the same result was discovered in the 1960s by Professor Gilbert Stork. Laird at 477: 2:16. Dr. Laird also testified that a person of ordinary skill in the art would know of other alternative ways in which to prepare the compounds used in Example 20. Laird at 480: 18-22.

B. Background: ACE-Inhibitors Generally

The drugs discussed in this case, including Ramipril, are all "ACE inhibitors." ACE stands for "Angiotensin Converting Enzyme." It is an enzyme in the human body that can bind with a compound known as Angiotensin I to produce Angiotensin II. This conversion increases blood pressure by constricting blood vessels. ACE inhibitors such as Ramipril bind with ACE to prevent this conversion from occurring, and the result is lower blood pressure. There are currently ten ACE inhibitors on the market in the United States. Mosberg at 1491.

ACE inhibitors began to be developed in the late 1960s, when scientists began studying [*22] the venom of the Brazilian Viper because it was known reduce to blood pressure. The venom is made up of several amino acids bound together with all six stereocenters in the (S) configuration. The active compound scientists isolated that reduced blood pressure was known as BPP[5a]. Based on this compound, the pharmaceutical company Squibb succeeded in developing Captopril, the first man-made ACE inhibitor. They did so by cutting off part of the BPP[5a] chain and adding a sulfur atom at the end. The development of Captopril was an early success of "structure-based drug design," which is the idea that knowing something about the structure of a compound -- in this case, a natural compound -- allows chemists to design compounds having similar effects. Ganem at 165: 21-23. Captopril has a single five-membered proline ring connected to a side chain with a sulfur atom. It also has two chiral centers, both of which are in the S-configuration.

While Captopril was a tremendous innovation, the presence of the sulfur atom was responsible for allergic reactions in some individuals. In response to this problem, Merck developed Enalapril, removing the molecule containing the sulfur atom and replacing [*23] it with a different molecule. Enalapril has a five-membered proline ring structure. It also has three stereocenters. All of them are in the (S) configuration. Ganem at 181: 3-4. As one of what could be considered the "third-generation" of ACE inhibitors, Ramipril was created by modifying Enalapril. Ramipril differs from Enalapril in that it has an additional ring structure, giving Ramipril two additional chiral centers. Accordingly, Ramipril has a total of five chiral centers. Ramipril's spatial orientation is discerned by these five chiral centers.

When a molecule, such as Ramipril, has five chiral carbons, there are thirty-two (32) possible configurations of the chiral carbons. In other words, because it has five chiral carbons, Ramipril has five stereocenters with each of the centers determining the molecule's shape. The number one center could be in S, with the rest of the centers in R. Another possibility is that centers one and two could be in S, with centers three, four, and five in R. In this way, thirty-two (32) three-dimensional shapes of the Ramipril molecule are possible (2<5> = 32).

The parties agree, and the Court **FINDS**, that the preferred combination of a single [*24] molecule of Ramipril has one specific chiral combination, the "S-configuration." This means that all five chiral centers are in S. This also means that a single Ramipril molecule with the "all S" or "5-S" configuration has a certain shape. The five chiral carbons in a single Ramipril molecule are indicated with an asterisk in the depiction of the molecule below:

[See formula in print version]

Because the thirty-one (31) other possible versions of Ramipril molecules have the same constituent atoms but are arranged differently based on their chiral carbons, the thirty-one (31) other possible versions of Ramipril are the "stereoisomers" or "isomers" of Ramipril in the 5-S configuration.

C. The '722 Patent

1. Ramipril Substantially Free of Other Isomers

Issued on October 29, 1991, the '722 patent is entitled "Cis, Endo-2-Azabicyclo [3.3.0]-Octane-3-Carboxylic Acids, A Process for Their Preparation, Agents Containing These Compounds And Their Use." It covers Ramipril "substantially free of other isomers." Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are the inventors of the '722 patent. The '722 patent has the following five [*25] claims:

Claim 1: A compound of the formula

[See formula in print version]

or a physiologically acceptable salt thereof, wherein R2 is hydrogen, methyl, ethyl, or benzyl, and wherein hydrogen atoms on the ring carbon atoms in the 1 - and 5-positions are in the cis-configuration relative to one another, the carboxyl group on the ring carbon atom in the 3 - position is in the endo position relative to the bicyclic ring system, and the chirality centers in the chain and on the ring carbon atom in the 3-position all have the S-configuration, said compound or salt being substantially free of other isomers.

Claim 2: A compound or salt as in claim 1 which is N-(1-S-carboethoxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicy acid or a salt thereof.

Claim 3: A compound or salt as in claim 1 which is N-(1-S-carboxy-3-phenyl-propyl)-S-alanyl-cis,endo-2-azabicyclo-| acid or a salt thereof. [Note: this claim is not at issue in this case.]

Claim 4: A hypotensive composition for reducing blood pressure comprising a hypotensively effective amount of a compound or salt as in claim 1 and a pharmaceutically [*26] acceptable excipient therefor.

Claim 5: A method for reducing blood pressure in a patient which comprises administering to said patient a hypotensively effective amount of a compound or salt as in claim 1.

Aventis/King has asserted claims 1, 2, 4 and 5 against Lupin. Because all the claims rise or fall with the validity of claim 1, claim 1 has been the parties' and the Court's focus.

D. Chronology of Events Leading to the '722 Patent

There is little question that Merck's introduction of Enalapril spurred the development of Ramipril. There is also little question that Aventis (previously known as Hoechst) [6] and Schering Corporation were competing with each other to develop Ramipril first. The following chronology thus indicates both Aventis' efforts as well as the Schering Corporation's efforts to develop and patent Ramipril.

6 As the Court reviews the chronology of events leading to the '722 patent, the Court will generally use "Aventis" or "Aventis/Hoechst" for "Hoechst" in an effort to keep the parties straight and avoid confusion.

[*27] The question always in dispute in these cases, apparently, is who invented what and when. This case is no exception. Of particular relevance in this case is what Dr. Elizabeth Smith, a chemist employed by Schering Corporation, invented or did not invent. Also of importance is the operability of what is known as "Example 20," which appears in what Lupin calls the "Schering References," a series of patents and patent applications that include Application No. 199,886 (the '886 application), Application No. 06/258,484 (the '484 application), and United States Patent No. 5,348,944 (the '944 patent). Ganem at 306-07. Another issue of contention involves United States Patent No. 4,587,258, which Aventis licensed from Schering and, at the least, included a compound that "encompassed" Ramipril. Finally, as several patent applications are at issue, the Court observes that chemistry applications and patents themselves are like puzzles -- one compound will be defined in one section, while another section incorporates this compound into its formula. Consequently, in order to understand what a specific example in a patent discloses, it is often necessary to refer back to other portions of the patent [*28] based on the example's instructions. Although, at times, this makes for tedious reading from the Court's perspective, it is a way for inventors to avoid repeating the same formulas over and over throughout a patent.

1. Enalapril

In June of 1980, Enalapril's structure was first announced at a scientific conference held in Troy, New York. Ganem at 183: 5-8. On June 25, 1980, Merck's European patent application for Enalapril was published. Def.'s Ex. 696.

Enalapril's structure was also published in an article titled "A New Class of Angiotensin-Converting Enzyme Inhibitors" in the prestigious journal Nature in November 1980. Def.'s Ex. 320. Dr. Ganem, Lupin's expert, whom the Court found credible, testified that one of the key points a person of ordinary skill in the art would take away from the article was that, if the all-S configuration in Enalapril was not followed, "significant potency was lost . . . about a 700-fold difference." Ganem at 187: 20-24. More specifically, the article concluded that the "S,S,S for Enalapril was seven hundred times more potent than the S,S,R" version of Enalapril. Ganem at 187-88: 25-1.

Dr. Ganem also testified that the article described [*29] how Merck prepared the S,S,S, and S,S,R versions, which are diastereomers, using a type of chromatography and crystallization process. Ganem at 192: 11, 22; 194: 1-8. In addition, he concluded that a person with ordinary skill in the art as of the time the article was published would have been capable of performing these processes. Ganem at 194: 21-22. He also stated that, after looking at Merck's patent for Enalapril, one with ordinary skill in the art would understand that the (S)-configuration was preferred and that chromatography crystallization worked to obtain a pure compound. Ganem at 207: 1-14.

2. Schering -- Dr. Smith's First and Second Disclosures

Dr. Smith, a chemist for Schering Corporation who was working on ACE-inhibitors, became aware of Enalapril after attending the June 1980 Merck conference and testified, by means of deposition testimony read in open court, it gave her "very interesting information." Smith at 756: 16. She stated her "first thought was to modify the ring structure . . . and then afterwards work on the side chains." Smith at 757: 7-9. She also testified: "I think it was stressed enough at the meeting that the (S)-configuration in the side chain [*30] was important for the best, you know, the more potent compounds."

Smith at 758: 6-8. On June 20, 1980, a few days after the conference, she prepared a written disclosure in her lab notebooks of the compounds she invented modifying the proline structure in Enalapril. Smith at 761: 16; Def.'s Ex. 1101. Dr. Elijah Gold's signature appeared beneath Dr. Smith's on the disclosure. Smith at 761: 23.

Specifically, with respect to a compound identified on page SCH00317 of her lab notebook, Dr. Smith testified that the disclosure encompassed the compound Ramipril. Smith at 762: 19. Regarding the stereochemistry of the compound, she testified:

> A: On 3 it is defined in the proline under, under Z, where that carboxylic acid is attached. The stereocbemistry is not defined.
>
> Q: Do you have any understanding as to whether the carboxylic acid group in structure 3 [is] in the *endo* position?
>
> A: Carboxylic acid is in 3, it's in the, in the op -- and let's see. Endo's -- gosh. Endo is down.
>
> Okay. Carboxylic acid is in the same position as it would be in the proline, in the S position.

Smith at 762-63: 20-25, 1-5. She also noted that, on the bottom of page SCH00317, [*31] the disclosure "contemplates all possible stereoisomers." Smith at 766: 4-6.

> Q: Okay. Now when you stated, quote, contemplates all possible stereoisomers, end quote, you weren't contemplating that these compounds were going to be together in a substance that had all of the isomers in it, were they?
>
> A: No, we didn't, we didn't intend to have a compound with all of them in there.
>
> Q: Right. Ideally it would have the one most-potent isomer in it?
>
> A: It was hoped that it would be narrowed down. Well, one likes to have a commercial compounds that, you know, have appropriate stereochemistry to give, you know, the maximum activity, and one doesn't want other stereoisomers in it.

Smith at 766-67: 16-25, 1-2.

Dr. Smith made her second disclosure of the "5,5 fused ring system" on August 1, 1980. Id. at 763: 16-19. She testified that the "Z group" in the disclosure corresponded to the side chain for Captopril and that the second side chain would be for Enalapril. Smith at 763-64: 25, 1-2. Dr. Smith also testified that she had an expectation that the compounds she was creating would lower blood pressure better than Enalapril did. Smith at 764: 24-25. She stated [*32] that for two years, beginning on June 20, 1980, her primary focus was preparing compounds that satisfied the descriptions in her disclosures. Smith at 768: 15-19.

3. Schering's '886 Application

On October 23, 1980, Schering Corporation filed U.S. Patent Application No. 06/199,886 (the '886 application). Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. The '886 application is a part of a chain of applications leading to Schering's '258 patent and Schering's '944 patent.

Dr. Smith testified that, on page five of the application, the ring structure depicted encompassed 5,5 fused ring systems. Smith at 771: 2-5. Looking at page eleven of the application, Dr. Smith explained that silica gel chromatography, reverse phase chromatography, or fractional crystallization methods were the methods used to separate the "diastereomeric products result[ing] from the synthetic procedures." Smith at 771-72: 16-17, 1-3. Turning to page twelve of the application, Dr. Smith testified that the amino acid structures found in formula one were "preferred in the S configuration," stating this preference related to the fact that "Enalapril had the centers in the S configuration, [*33] and it would be important that our compounds have the S configuration in these part structures." Smith at 772: 14-16. She also noted that a third structure on page twelve, referencing R4 and R5, connected to form 5,5 fused ring systems. Smith at 772: 22. Finally, turning to Example 20 of the application on page 22, she testified that the title compound of the Example contained Ramipril. Smith at 773: 5. Example 20 of the '886 application reads as follows:

> 2-[N-(1-Carboethoxy-3-phenylpropyll)-(S)-alanyl]octahydrocycl acid

> A. Substitute octahydrocyclopenta[b]pyrrole (prepared by reduction of 2-ketooctahydrocyclopenta[b]pyrrole in tetrahydrofuran with lithium aluminum hydride) for octahydroisoindole in Example 18 A to obtain octahydrocyclopenta[b]pyrrole-2-carboxylic acid.
>
> B. Use ethyl octahydrocyclopenta[b]pyrrole-2-carboxylate (prepared by esterification with the ethanol of the acid prepared as described in paragraph A) in place of ethyl octahydroindole-2-carboxylate in the procedure described in paragraphs B through E of Example 1 to give the title compound.

Def.'s Ex. 15 at LUPRAM 001635. Dr. Smith also stated [*34] she "did not synthesize the 5,5 carboxylic acid," but, at some point, "assemble[d] . . . a compound which contained Ramipril . . . in the 5(S) configuration" as part of a mixture containing other isomers. Smith at 773: 14-16. The Court **FINDS** that the first disclosure of Ramipril as part of a mixture occurred on October 23, 1980, which is the filing date of the '886 application. Because both Schering's '258 patent and its '944 patent claim priority to the '886 application, the Court also **FINDS** that these patents are entitled to an effective filing date of October 23, 1980.

4. Schering -- Dr. Smith's Sample SCH 31925

Dr. Smith testified that, on February 12, 1981, she prepared a compound, referred to as "Sample SCH 31925," that included the Ramipril molecule, which she recorded in her lab notebooks. Smith at 775: 6-9; 785: 12. According to Dr. Smith, SCH 31925 resulted in two diastereomers, one in the all-(S) configuration and the other with an R at the end of the side chain. She did not separate the mixture. Smith at 889: 17-18; 891: 7-8. Dr. Smith believed she was the first person to make Ramipril in a diastereomeric mixture. Smith at 893: 10-11. Dr. Neustadt [*35] confirmed that Dr. Smith made Ramipril in a diastereomeric mixture and did not separate it. Neustadt at 1099: 24; 1118: 12-21. He also testified, however, that "[w]e had an expectation that the material in the (S) configuration would be most potent." Neustadt at 1122: 7.

Dr. Smith also testified that she used Raney nickel instead of the sodium cyanoborohydride reaction provided for by Example 20. Smith at 824: 4-5. When asked why she did this, she replied: "[o]ne uses sodium cyanoborohydride, and one uses Raney nickel." Smith at 824: 9-10. She maintained, however, the SCH 31925 was made by following Example 20 from start to finish, stating "it was made using a different condition[] for reductive alkylation." Smith at 824: 14-15. The Court is not disturbed by Dr. Smith's admission that she tweaked the process of Example 20. After hearing testimony from various experts -- all of whom, it appears, feel free to tweak procedures as they see fit -- the Court has no trouble **FINDING** that persons of ordinary skill in the art often tweak experiments based on their understanding of the literature and/or their experience. Accordingly, the Court **FINDS** that, based on the steps [*36] outlined by Example 20 in the '886 patent and with some tweaking done by one with ordinary skill in the art, Dr. Smith made a diastereomeric mixture of Ramipril, with one part being in the all-(S) configuration (S,S,S,S,S) and the other having an R at the end of the side chain (S,S,S,S,R). The Court has little doubt that the process Dr. Smith used was not an easy one, see infra, but is satisfied that she, indeed, made the compound pursuant to the instructions provided for in Example 20. The Court also **FINDS** that she did not separate the diastereomeric mixture.

The Court also **FINDS** that Aventis concedes that the title of Example 20, "if operable," would result in "a mixture . . . of at least eight compounds at the end." Winkler at 1580:17; 1582:1. See also Mosberg at 1260: 21-1261: 8 (stating that Example 20 describes a compound that "embraces eight stereoisomers"). Dr. Ganem, Lupin's expert, also agreed that the title compound of Example 20 embraced eight isomers. Ganem at 396: 19-25; 397: 1-4. The Court notes that all of these conclusions refer only to what the title of Example 20 indicates. Laird at 631: 18-632: 13. The Court is persuaded by Dr. Laird's testimony, [*37] Lupin's expert, that, while the title encompasses eight isomers, the actual "experimental" that follows instructs that *cis, endo* starting compound should be used -- and this leads to four products that may then been separating using chromatography methods available to one of ordinary skill in the art. Laird at 630: 17; 631: 12-13. Indeed, Dr. Mosberg, Aventis' expert, which the Court found somewhat credible even though he refused to

directly answer many of the Court's questions and advocated a little too much for the side which was paying for his services, testified that, "even though the title of Example 20 allows for the possibility of eight isomers, for all practical purposes only four could actually be made by following the example" because "the example produces only *cis* bridgehead atoms." Mosberg at 1424: 14-19. Given all of this, and given that Dr. Smith, as a third party and unlike any of the other experts testifying in this case had nothing to gain by testifying one way or the other, the Court has little difficulty finding that Dr. Smith truthfully stated she created a diastereomeric mixture of two compounds of Ramipril, with one part being in the all-(S) configuration [*38] (S,S,S,S,S) and the other having an R at the end of the side chain (S,S,S,S,R).

5. Schering's '484 Application

On April 28, 1981, Schering Corporation filed United States Patent Application No. 06/258,484 (the '484 application). Again, Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. Def.'s Ex. 16. The '484 application is a continuation-in-part of the '866 application. Id. It contains the same Example 20 as the '886 application. Def.'s Ex. 16 at LUPRAM 001300-01. The '484 application is a precursor to Schering's '258 patent and '944 patent.

6. Aventis -- Dr. Teetz

Dr. Volker Teetz, a chemist for Aventis, testified, by means of deposition testimony read into the record, that he synthesized Ramipril on October 28, 1981. Teetz at 966: 1-4. According to Dr. Teetz, the first synthesis he created was a mixture, from which "using [his] knowledge from today," he then isolated an all-(S) configuration of Ramipril as the "main product." Teetz at 967: 13-17. He stated he separated the diastereomeric mixture using column chromatography. Teetz at 974: 22-25.

Dr. Teetz also testified that he was asked to replicate the Schering patent application [*39] exactly to see if it would work. He concluded that Example 20 did not work. The Court first observes that Dr. Teetz testified that, when he tried to follow the Schering patent application, he recorded his results in private notebooks, which he destroyed after leaving the company. Teetz at 964:1-20; 980: 12-18.

> Q: So am I to understand that on several occasions you attempted to exactly reproduce the Schering synthesis, but on none of those occasions did you put any entry of those attempts in the official lab notebooks?
>
> A: As far as I can recall, yes.
>
> Q: The private notebooks that you put the attempts to exactly reproduce the Schering synthesis in, were those the same notebooks you destroyed in 1999?
>
> A: Yes. At that point in time in no longer seemed important to me to keep any documentation after 20 or 25 years.

Teetz at 980-81: 19-25, 1-3. After a two-week bench trial in which the Court heard from a variety of experts in chemistry, one thing is clear: keeping private notebooks with important information and then throwing them away is not normal practice for chemists. Dr. Smith's notebooks reveal that she not only carefully dated and recorded her results, [*40] but that she also found a witness to sign the appropriate notebook page whenever she created what she thought was an important compound. See supra at II.D.2. While keeping private notebooks might be considered suspect enough, Dr. Teetz also did not even consider returning them to the company he worked for when he left the company but destroyed them instead. These notebooks just happen to contain his attempts to exactly reproduce the Schering synthesis, which he claimed did not work and which was highly contested by Aventis throughout the 1980s before the PTO. The notebooks he kept for his company, in contrast, were all properly dated and preserved. [7] The Court consequently cannot credit his testimony with respect to Example 20. It also does not accept his testimony that he created Ramipril in the 5(S) configuration "substantially free of other isomers" in 1981 as Aventis contends, given that this phrase was not introduced with respect to Aventis' patent applications until September 29, 1988 (after the PTO rejected Aventis' patent applications several times) and that claims 19-23, which became claims 1-5 of the '722 patent were not added until October 9, 1984. See infra II. [*41] D.13. The Court does **FIND** that Dr. Teetz made a compound that encompassed Ramipril with other isomers, which was included in Aventis' European patent application and is

described immediately below.

7 Negative evidence, unfortunately for Aventis, leads to a positive conclusion.

7. Aventis' German Patent Application No. 3143946

On November 5, 1981, Aventis filed German Patent Application No. 3143946. Pl.'s Ex. 1. Dr. Teetz testified that Example 1 of the patent produced Ramipril in the 5(S) configuration. Teetz at 1036: 7-10, 20-21. He went on to state that the product was "practically pure" and "substantially pure." Teetz at 1037: 13-20. As noted supra, the Court gives no credence to Dr. Teetz's testimony, particularly with respect to his contention that, at the outset, he made Ramipril in the 5(S) configuration substantially free of other isomers. The Court is also not convinced that the inventors were even interested in such a compound -- the Court notes that Dr. Scholkens, another inventor [*42] working with Dr. Teetz, testified that he did not have "any understanding as to when the presence of other isomers in a Ramipril composition can have a material impact on the drug's therapeutic performance." Scholkens at 1086: 8-11. Dr. Scholkens also stated that, when he applied for the '722 patent, he had no "vision of how isomeric purity could impact the performance of [R]amipril." Scholkens at 1087: 9-12. Is the Court to believe that Dr. Scholkens, who was working with Dr. Teetz, did not know what Dr. Teetz was doing? Who's fooling whom. [8] The Court rejects Dr. Teetz's testimony as to his assertion he made Ramipril in the 5(S) configuration substantially free of other isomers.

8 Not me.

There is little question, however, that this application was part of a chain of patent applications that lead to the '722 patent. The Court **FINDS** that the '722 patent is entitled to a foreign priority date of November 5, 1981. The Court does not find, however, that this application disclosed "Ramipril in the 5(S) [*43] configuration substantially free of other isomers." The Court notes that the 5(S) configuration apparently was not claimed until October 9, 1984, when PTO noted that Aventis "now claim[ed] the *cis* compound exclusively," see Def.'s Ex. 100 at LUPRAM 000179-80, and that the phrase "substantially free of other isomers" was not introduced with respect to Aventis' patent applications until September 29, 1988 (after the PTO rejected Aventis' patent applications several times).

8. Schering's "Neustadt Application"

On June 5, 1982, Schering filed European Patent Application No. 50,800 (the "Neustadt Application"). Again, Elijah Gold, Bernard Neustadt and Elizabeth Smith were listed as the inventors. This patent application also contains the Example 20 found in Schering's '886 application. Def.'s Ex. 14 at LUPRAM 001865.

9. Aventis' '757 Application

On November 3, 1982, Aventis filed U.S. Patent Application No. 06/438,757 (the '757 application). Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens were listed as the inventors. Def.'s Ex. 100. The '757 application is a precursor to Aventis' '722 patent.

10. Aventis' '081 Application

[*44] On March 21, 1983, Aventis filed U.S. Patent Application No. 06/477,081 (the '081 application) as a continuation-in-part of the '757 application. Again, Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens were listed as the inventors. Def.'s Ex. 100. The '081 application is a precursor to Aventis' '722 patent.

11. PTO Office and Advisory Actions

On April 6, 1984, the PTO rejected claims 1-10, 16, 17 (claims 11-15 were withdrawn) of Aventis' '757 application as "being unpatentable over [Schering's] Neustadt European 50,800" (the Neudstadt patent). Def.'s Ex. 100 at LUPRAM 89-90. The Examiner stated:

> Note particularly compounds on pp. 95-96 -- per-hydropenta-pyrrole and the process of claim 10(e). The teachings of Neustadt encompass compounds claimed herein and are of common use with those claimed herein. Hence, claimed invention must be deemed prima facie obvious over Neustadt.

Id. at LUPRAM 90.

On May 2, 1984, the PTO rejected claims 1-8, 10, 11, and 18 of Aventis' '081 application (claims 9, 12-17 were withdrawn). The claims were rejected under 35 U.S.C. § 112 for failing to describe in clear [*45] terms

to enable a person of ordinary skill in the art to make the compounds; under 35 U.S.C. § 103 for being obvious with respect to Schering's Neustadt patent; and under 35 U.S.C. § 103 for being obvious under the teachings of two other patents not involved in this case, the "Hoefle" and "Harris" patents. Id. at LUPRAM 000158-160.

12. Schering's '390 Application

On July 30, 1984, Schering filed U.S. Patent Application No. 635,390, which eventually issues into U.S. Patent No. 4,587,258 (the '258 patent). It is a continuation-in-part of the '484 application.

13. PTO Action

On October 9, 1984, in response to the May 2, 1984 action rejecting its claims, Aventis filed an Amendment to its '081 application, cancelling claims 1-18 and adding claims 19-23. Id. at LUPRAM 000163. Claims 19-23 ultimately become, with some modifications, claims 1-5 of the '722 patent. Aventis also enclosed a Declaration from Dr. Bernward Scholkens, one of the inventors listed on the '081 application, to contest the Examiner's rejection based on obviousness. Id. at LUPRAM 000169. In his Declaration, Dr. Scholkens indicated that the invention [*46] in the '081 patent had an ACE-inhibiting activity about three times greater than Enalapril when given to dogs through intravenous injection and consequently was "far superior." Pl.'s Ex. 280 at A000115; Scholkens at 1081: 18-22 (emphasis added). This, according to Aventis' amendment, was a "surprising and unexpected" result. Def.'s Ex. 100 at LUPRAM 000169.

Although not included in his Declaration, Dr. Scholkens, however, testified in this case that Ramipril and Enalapril were "approximately equipotent" after intraduodenal administration. Scholkens at 1082: 1. When asked why he did not include the information about the results from intraduodenal administration as opposed to only including the results from intraveneous administration in his Declaration, Dr. Scholkens stated "the declaration is not a scientific paper." Scholkens at 1085: 21.

> Q: What does that have anything to do with it?
>
> A: I think there are clear-cut rules for a scientific paper because it's written for scientists, and here we are talking for a document which is, as you said, not for scientists but for the Patent Office.
>
> Q: You don't think a patent officer might not get confused that when [*47] you're saying that Compound 4 [Ramipril] is far superior to Compound 1 [Enalapril] they might conclude that you're extrapolating that conclusion to all species or all methods of administration?
>
> A: I'm not the patent officer, and I have to rely on his judgment.

Scholkens at 1085: 22-25; 1086: 1-6.

On November 8, 1984, Aventis filed a Supplemental Amendment, which amended Claim 19 by adding a new formula and including declarations by Dr. Urbach and Dr. Paulus. Def.'s Ex. 100 at LUPRAM 000176-000177.

On December 18, 1984, the PTO rejected claims 19-23 of Aventis' '081 application. With respect to its obviousness determination regarding two other patents not involved in this case, the "Hoefle" and "Harris" patents, the PTO withdrew its determination based on Dr. Scholkens declaration. Def.'s Ex. 100 at LUPRAM 000179. The PTO nevertheless maintained, however, its determination of obviousness with respect to Schering's Neustadt application. The Examiner also stated:

> Applicant now claims the *cis* compound exclusively. That compound is not taught in the first priority document. Since the claims as now drawn claims, but the earliest priority document does not disclose, [*48] the *cis* isomer, applicant must rely on the later priority document. Hence, this rejection is maintained for reasons of record. Neustadt at p. 23 indicates existence of enantiomers and diastereomers and means of separation. See also p. 26 where the *cis* project is specifically mentioned.

Def.'s Ex. 100 at LUPRAM 000179-180.

On March 15, 1985, Aventis filed a Request for Reconsideration of the Examiner's decision to reject claims 19-23 of the '081 application. Def.'s Ex. 100 at

LUPRAM 000182. On April 17, 1985, the Examiner issued an Advisory Action stating the request did not overcome the obviousness rejection. Id. at LUPRAM 000184. On June 3, 1985, Aventis filed another Request for Reconsideration because it "fail[ed] to take into consideration the Paulus and Urbach Declarations filed with the Supplemental Amendment of November 8, 1984 establishing a stereochemical difference between the claimed compounds and those of Neustadt." Def.'s Ex. 100 at LUPRAM 000187-188. Aventis included with its Request further declarations from Dr. Urbach and Dr. Paulus, urging that "the *cis*, endo form of the compounds of the invention and their distinction over the Neustadt reference [*49] of record [had been] established." Id. at LUPRAM 000188, 190.

On July 2, 1985, Aventis appealed the Examiner's December 18, 1984 decision. Def.'s Ex. 100 at LUPRAM 000192. On July 22, 1985, the Examiner again issued an Advisory Action rejecting claims 19-23. Def.'s Ex. 100 at LUPRAM 000193.

14. Aventis' '284 Application

On November 19, 1985, Aventis filed U.S. Patent Application No. 06/799,284 (the '284 application), which is a continuation of the '081 application. Pl.'s Ex. 4. Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id.

15. PTO Action

On March 20, 1986, the Patent Examiner rejected claims 19-23 of Aventis' '284 application. Def.'s Ex. 100 at LUPRAM 000210. Specifically, the Examiner found the claims "anticipated by Gold/Neustadt," explaining that "Neustadt is parent application to Gold." Id. at LUPRAM 000211.

16. Schering's '258 Patent

On May 6, 1986, Schering's Patent No. 4,587,258 (the '258 patent or "Gold patent") issued. Elijah Gold, Bernard Neustadt, and Elizabeth Smith are listed as inventors of the patent. Def.'s Ex. 306. The '258 patent is a continuation-in-part [*50] of the '484 application, which was a continuation-in-part of the '649 application, which was a continuation-in-part of the '886 application. The Court **FINDS** that the '258 patent is entitled to the effective filing date of the '886 application, which is October 23, 1980.

The '258 patent did not have an Example 20; rather, the title of Example 3 in the '258 patent indicated that, by following the example indicated, some measurable amount of Ramipril in the 5(S) configuration was made. Smith at 808: 16-23. [9] Dr. Smith also testified that the Example 20 preparation set forth in the '484 application corresponded to the process set forth in the '258 patent in Example 1, part A. Smith at 806: 9-18.

> 9 The title of Example 3 is 1-[N-(1(R,S)-Carboethoxy-3-Phenylpropyl)-(S)-Alanyl]-Cis, Endo-Octahydrocyclopenta[b]pyrrole-2(S)-Carboxylic Acid. Def.'s Ex. 306 at A 053262.

In addition, Dr. Smith testified that claims 1, 2, 3, 5 and 6 of the '258 patent involved Ramipril. Id. at 810-13. Claim 1, according to [*51] Dr. Smith, allowed for "a lot of variations at R1, R3, and R6" that are "one part of a family of compounds." Id. at 812: 9-12. It encompassed Ramipril "with the appropriate stereochemistry." Id. at 810: 20. With respect to Claim 2, she testified:

> Q: . . . And, similarly, does the compound description that's presented in Claim 2 of the '258 patent, does this description also encompass the compound ramipril?
>
> A: Yes.
>
> Q: And based on the description of the material as being a cis, endo isomer, would that indicate that within the ring structure itself the stereoconfiguration would be S,S,S?
>
> A: They are all hydrogens on the same side.
>
> Q: And since the carboxylic isomer is S would that also mean that the stereoconfiguration of the two carbons at the ring fusion would also have to be S?
>
> A: Yes.

Smith at 810: 21-24; 811: 1-7. Dr. Smith then explained that claim 3 corresponded to Ramipril. Smith at 811:13. Claim 5 was the diacid version of Ramipril, which,

according to Dr. Smith, refers to the fact that Ramipril gets converted to diacid when it is ingested. Smith at 811: 18-23. Claim 6 describes the compound Ramipril as a hydrochloride salt. Smith [*52] at 811: 9-10. Dr. Smith also testified that compound SCH 31925 and the compounds set forth in the '258 patent would lower blood pressure in the same way. Smith at 814:3-8. The Court **FINDS** that the '258 patent discloses the same mixture as SCH 31925, which was a diastereomeric version of Ramipril, with one part being in the all-(S) configuration and the other having an R at the end of the side chain (S,S,S,S,R).

17. The Taylor, Becker, Barton and Urbach Declarations

On September 18, 1986, Aventis filed the Declaration of Dr. Edward Taylor, an expert employed by Aventis to repeat the synthesis of the title compound as described in Example 20 of the Neustadt application, with the PTO. Id. at LUPRAM 000215-16. Dr. Taylor concluded that the compound could not be made according to the procedure described in Example 20. Id. at LUPRAM 000216.

On November 18, 1986, Aventis filed the Declaration of Sir Derek Barton, an expert employed by Aventis to repeat Example 20 in the Neustadt Application, with the PTO. Id. at LUPRAM 000232. He also concluded that Example 20 was not operable. Id. Aventis also filed the Declaration of Dr. Becker, who concluded that Ramipril [*53] with a mixture of stereoisomers would result from Example 20 of the '944 patent if made in a different way from the teaching of Example 20. Pl.'s Ex. 299; Mosberg at 1366: 17-23.

The parties' experts also testified as to whether Example 20 was operable. Dr. Mosberg, an expert for Aventis who repeatedly said Example 20 did not work, notably was not able to give his opinion on whether a person of ordinary skill in the art having an understanding of the prior literature would have been able to follow Example 20. Mosberg at 1366: 1-23. Dr. Winkler, an expert for Aventis, whom the Court found credible until he refused to interpret the difference in blips on a nuclear magnetic resonance printout obvious even to the Court because such interpretation would not have been advantageous for Aventis, see Winker at 1591-1600, also stated that Example 20 did not work. Dr. Winkler, in addition, only provided testimony with respect to Dr. Crimmins, who testified in litigation between Aventis and another generic company in 2003 about the operability of Example 20. Dr. Crimmins did not testify, by means of deposition or otherwise, in this case.

Dr. Laird, for Lupin, testified that Example 20 was [*54] operable and pointed out problems with the declarations Aventis' experts submitted stating otherwise. With respect to Dr. Barton's declaration, see Def.'s Ex. 657, Dr. Laird testified that the declaration indicated that Dr. Barton carried out the mercuric acetate oxidation process only once. Laird at 485:10-12. He then testified that a person of ordinary skill in the art would "hardly ever" do just one experiment; rather, when a reaction is described in the literature, a person of ordinary skill would assume the author's honesty as well as assume he performed the experiment incorrectly or the quality of his reagents were at issue. Laird at 486:21-26; 487:1-2. Moreover, Dr. Laird pointed out that Dr. Barton diverged from Leonard's process in several respects. First, after the white precipitate is formed and filtered, he added sodium sulfide instead of hydrogen sulfide, although Dr. Laird noted this did not alter the overall process. Laird at 489: 15-16; see also supra II.D.5 for a description of Leonard's process. Second, instead of following Leonard's distillation of product procedure, Dr. Barton added benzene and boiled out the water. Laird at 490: 1-5. This resulted in a [*55] benzene solution that he then boiled off, which left very little product. Dr. Barton also did not characterize what this resulting product was. Laird at 492: 21-23. Thus, from Dr. Barton's data, it is unknown whether the oxidation he conducted made the imine from the amine. Laird at 504: 20-24. Accordingly, the Court **FINDS** that Dr. Barton's declaration does not show that Example 20 does not work, but the Court **FINDS** that Example 20 could work by a chemist with ordinary skill in the art.

With respect to Dr. Taylor's declaration, see Def.'s Ex. 201, Dr. Laird testified that, again, only one mercuric acetate oxidation on the starting material in Example 20 -- octahydrocyclopentapyrrole -- was carried out. Laird at 525: 15-18. Moreover, Dr. Laird testified that the declaration indicated that the experiment was not conducted very well. Laird at 525:22-24. Dr. Laird first related that Dr. Taylor began by following the procedure outlined in Example 20 -- mixing the starting material and mercuric acetate in ten percent acetic acid solution and heating under reflux (boiling). Laird at 526:17-19. Dr. Taylor reported a yellow solution and a precipitate

forming within two hours. [*56] Laird at 526: 20-21. He then refluxed for 20 hours and extracted the yellow water solution with a solvent. Laird at 526: 23-25. However, after obtaining the organic solvent layer, which was dried and evaporated, the remaining yellow aqueous layer was not analyzed. In Dr. Laird's opinion, the aqueous layer should have been analyzed because the imine product, if formed, would have been found there. Laird at 527:5-12. Dr. Laird explained that, because the water layer is acidic,

> What he should have done was to basify the water layer to make it basic and then extract it, and that's when you would get the imine form. That's the teaching of the Leonard papers, the Bonnet [paper]. . . that you have to basify to get the product to come into the organic layer.
>
> So it's not surprising he didn't get any yield . . . .

Laird at 527: 20-25. Dr. Laird then pointed to a paper by Professor Leonard describing mercuric acetate oxidations, see Def.'s Ex. 349, which describes how, when Professor Leonard did what Dr. Taylor did, no yield occurs. Laird at 529:12-13. However, when the aqueous layer is basified, the paper shows a thirty-four percent yield of the desired product. Laird [*57] at 520: 16-17. The Court **FINDS** that Dr. Taylor's declaration does not show that Example 20 does not work.

On November 14, 1986, Aventis filed with the PTO the declaration of Dr. Reinhard Becker. Pl.'s Ex. 299; Def.'s Ex. 100 at LUPRAM 000242. According to Dr. Mosberg, Aventis' expert witness, Dr. Becker compared Ramipril with a mixture of stereoisomers that would result from Example 20, "if Example 20 were operable," and Ramipril in the 5(S) configuration "substantially free of other isomers" in Aventis' '284 application. Mosberg at 1366: 17-19; 1368: 5-8. Before proceeding further, the Court is compelled to make the following observations about Dr. Mosberg's testimony. First, when Dr. Mosberg made this statement, the Court asked him how Dr. Becker could compare the two compounds if Example 20 wasn't operable. Dr. Mosberg replied that the compound was made "a different way." Mosberg at 1366: 22. The exchange proceeded with Dr. Mosberg not committing to an opinion as to whether one with ordinary skill in the art would have known how to make the compound understanding what the prior literature was, and the Court is inclined to believe he did not do so because it would have been [*58] adverse to Aventis. Mosberg at 1367: 22-23. This exchange only bolsters this Court's finding that one of ordinary skill in the art with an understanding of the prior literature would have been able to make Example 20, just as Dr. Becker was able to do so.

Second, the Court observes that Dr. Becker's Declaration says nothing about being "substantially free of other isomers." Dr. Mosberg says the compound compared is "substantially free" because the application at issue ultimately "resulted in the '722 patent, so that means Compound A, [R]amipril, made by that process is substantially free of other isomers." Mosberg at 1368: 5-8. This kind of circular logic ran throughout this litigation. Many times, Plaintiffs' argument appeared to be that, because the '722 patent included the phrase "substantially free of other isomers," then all the prior art and any testing or commercial success related to Ramipril necessarily related to the product being "substantially free of other isomers," which is not true.

In any event, Dr. Mosberg testified that Dr. Becker's results showed that "[R]amipril substantially free of other isomers [Sample A] is about three times more potent that the mixture [*59] of stereoisomers that would result from [E]xample 20 [Sample D] and that the onset of action is also quicker." Mosberg at 1368: 11-14. He also testified that one of ordinary skill in the art would not have that expectation. Mosberg at 1368: 20.

On cross-examination, however, Dr. Mosberg noted that the amount of 5(S) isomer in the Sample D -- the "mixture sample"-- was between a quarter to a third. Mosberg at 1406:10-11. He also agreed that Sample A -- the 5(S) compound substantially free of other isomers -- was "three times as concentrated . . . in [R]amipril" as Sample D. Mosberg at 1406: 12-14. The following exchange then occurred:

> Q: So why is it surprising to a person learned in the art that when you make a Ramipril sample that's three times more concentrated than another one, you get a potency reading that's three times as high?
>
> A: Because one of ordinary skill in the art at this time would have no expectation of the activity of the other isomers, the other three stereoisomers in

the mixture would have. I mean from today, from hindsight, it's very clear that that is what you would expect. But not until you actually have looked individually at all the isomers [*60] could you have that expectation.

The Court: So it really, what you're saying, am I to understand, that it depends on the dosage? You take 10 milligrams of something and you take 20 milligrams of something, 20 milligrams is more potent than 10?

A: I think that is generally true. I don't know it's always true.

The Court: . . . And what I want to question is if it were 30 milligrams versus 10, would you expect three times the potency generally? Not in this.

A: Generally if you haven't already maxed out the potency as a lower dose, then you would expect the potency to increase. It's not linear.

The Court: Well, ACE inhibitors, do doctors generally give greater amounts of milligrams in their tablets to people who have higher blood pressure?

A: I can't speak as an expert, but I think as a lay person, yes, if a lower dose isn't effective, a doctor would give a higher dose.

The Court: Why?

A: The understanding that more of the drug will have more of the effect.

Mosberg at 1406: 18-25; 1407: 1-25. Dr. Mosberg continued by saying that the Declaration itself demonstrated that, if Sample D -- the mixture -- was given in a 30 milligram dose, it would [*61] lower blood pressure as well as Sample A -- the substantially free -- in a 10 milligram dose. Mosberg at 1408: 6-9. The Court **FINDS** that, according to Dr. Mosberg, if Sample D had three times the concentration of the 5(S) isomer, it would perform the same as Sample A. Put simply, the more 5(S) isomer you have, the more potent the compound is. Given this obvious outcome, the Court therefore does not agree with Aventis that Dr. Becker showed that Ramipril in the 5(S) configuration substantially free of other isomers showed an "unexpected result" compared to Ramipril made from Example 20. The Court, however, is not convinced -- by clear and convincing evidence -- that Ramipril in the 5(S) configuration substantially free of other isomers is meaningless, as the parties agree that the 5(S) configuration is preferred.

On November 14, 1986, Dr. Hansjorg Urbach submitted a Declaration stating that the title compound of Example 20 in the Neustadt Application did not work. Def.'s Ex. 100 at LUPRAM 000249. Dr. Laird, Lupin's expert, reviewed the detailed experimental that Dr. Urbach presented in his declaration. Laird at 548: 19. He testified that Dr. Urbach stated that he obtained a mixture [*62] of Ramipril in the 5(S) configuration and its stereoisomer, the S,S,S,S,R compound, in a 65 to 35 ratio. Laird at 550: 15-18; see also Def.'s Ex. 17 at LUPRAM 000557 (Urbach Declaration). Although the title compound of Example 20, which has an "ethyl ester" and thus would require ethanol to be used as a solvent rather than methanol, Dr. Urbach, however, used a "mixture of methanol and ethanol." Laird at 558: 6-12. Dr. Laird noted that Example 1-E, which followed from Example 20, instructs that ethanol *or* methanol may be used, depending on the ester desired, but it does not instruct that a mixture be used. Laird at 559: 1-4. According to Dr. Laird, Dr. Urbach thus made Ramipril as part of a mixture following Example 20. Laird at 560:22. Dr. Laird also testified that, if the experiment was done correctly using only ethanol, it would have resulted in Ramipril and the ethyl ester, which would have been separable by chromatography. Laird at 562: 1-3.

On cross-examination, Dr. Laird agreed that Dr. Urbach stated in his declaration that he planned to discuss the "theoretical question of what would have been the result of Example 20 B," but went on to note that Dr. Urbach nevertheless [*63] went on to do it. Laird at 623: 5-8. It was then pointed out that Dr. Urbach did not perform Example 20A because he made a substitution. Laird at 624-25. Again, this only reinforces the Court's finding that chemists having ordinary skill in the art tweak as they make chemical compounds to achieve the result they seek. In other words, a good chemist learned in the art, if he wants to make the compound can, and, if he doesn't, he won't.

19. PTO Action

On December 9, 1986, the Examiner rejected claims 19-23 of Aventis' '284 application for being "anticipated by Gold U.S. 4,587,258" (the '258 patent). Id. at LUPRAM 000269-270. The Examiner noted that the Aventis urged that "Gold is not enabling," but observed that "a U.S. patent is presumed valid." Id. at LUPRAM 000271. [10] The Examiner invited the parties to participate in an interference proceeding. [11] Id.

> 10 Although Aventis told this Court on numerous occasions that it was not rehashing arguments made before the PTO about the enablement of Example 20 in the Schering References and the enablement of the '258 patent, the Court sees it otherwise. The PTO heard all of the arguments the Court heard and found that Schering invented Ramipril, at least as part of a mixture, first.

[*64]

> 11 "Section 135 of the United States Code, Title 35, governs patent interference proceedings, which are designed to determine whether two patent applications (or a patent application and an issued patent) are drawn to the 'same patentable invention' and, if so, which of the competing parties was first to invent the duplicative subject matter." Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington, 334 F.3d 1264, 1267 (Fed. Cir. 2003).

On December 12, 1986, the Examiner issued a Supplemental Response entering the Declarations of Dr. Becker, Dr. Taylor, and Dr. Burton. Id. at LUPRAM 000275. The Examiner maintained his rejections, stating:

> The declarations are not persuasive of inoperability since no averment is seen that declarants did not know of other means to make the named compounds of Gold . . . . More is required that simply showing Gold's compounds can not [sic] be made by the process disclosed by Gold. There is a burden on the junior to prove by a preponderance of the evidence the taught process could not have been made operative by persons of ordinary [*65] skill in the art with the teaching of the disclosure before him.

Id. (internal citations omitted).

19. Schering/Aventis License Agreement

On December 15, 1986, Aventis/Hoeschst and Schering Corporation entered into an agreement in which Schering granted Aventis a license under Schering's patent rights to produce pharmaceutical products containing Ramipril under the condition that Schering would be paid $ 500,000 upon execution of the agreement, $ 500,000 upon FDA approval to market the licensed product, and five percent of Aventis' net sales of Ramipril. [12] Pl.'s Ex. 317 at SCH 001463, SCH 001465. The term "licensed compounds" was defined to mean the following in Section 1.1.:

> 2-[N-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S, 3S, 5S)-2-oxabicyclo [3,3,0]octane-3-carboxylic Acid (Ramipril) and 2-[N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azab Acid (Ramiprilat) including their salts, hydrates and solvates.

Id. at SCH 0001461. Schering's Neustadt Patent (50,800), the '484 application, and the '258 patent were among the patents listed in Appendix A to be licensed by Aventis. Id. [*66] at SCH 001475.

> 12 The payments of $ 500,000 were to be credited against the royalties Schering received. Pl.'s Ex. 317 at SCH 001464.

20. PTO Action

On May 19, 1987, Aventis filed a Request for Reconsideration of the Examiner's rejection of claims 19-23 of the '284 patent. Def.'s Ex. 100 at LUPRAM 000278. Aventis specifically pointed out that the compounds of each of claims 19-23 "characteristically have five chiral centers, each of which is in the S-configuration." Id. at LUPRAM 000280. Aventis also stated:

> Compounds having this substituted ring structure and an appended sidechain on the ring nitrogen atom are show in the Gold '258 patent and are claimed in Claims 3-6 and 131-6, for instance. These Gold compounds, since they are cis, endo and

> have both chiral centers in the sidechain in the S-configuration, are also S,S,S,S,S compounds. Support for compounds of these specific steric configuration is to be found in Examples 3, 5, and 10 of the Gold patent with the synthesis of the compounds [*67] being supported by Examples 1 and 2.
>
> However, the Examiner will search in vain for a similar disclosure of these specific S,S,S,S,S compounds in any of the prior applications of Gold et al. indicated as being predecessor applications.

Id. at LUPRAM 000280-281. On May 27, 1987, Aventis communicated to the Examiner that they wanted an interference proceeding declared with respect to the '258 patent on "specific claimed isomers." Id. at LUPRAM 000285.

21. Interference Proceeding

On January 12, 1988, the Board of Patent Appeals and Interferences declared Interference No. 101,833 between Elijah Gold, Bernard Neustadt, and Elizabeth Smith, inventors of the '258 patent, and Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens, inventors of the '284 application.

On June 30, 1988, Dr. Jerrold Meinwald made a declaration stating that Example 20 worked and refuting the declarations made by Dr. Taylor and Dr. Barton that it did not. Def.'s Ex. 659A at SCH-001587, SCH-001595. Dr. Meinwald stated that Example 20 created yields of 32 to 35 percent of the desired product. [13] Def.'s Ex. 659A at SCH-001591. According to Dr. Laird, Dr. Meinwald [*68] got a mixture of isomers. Laird at 628:17. Dr. Meinwald then obtained an NMR spectra of the *endo* and *exo* isomers, which, in Dr. Laird's view, indicated that he separated them. Laird at 630: 6-8.

> 13 Dr. Meinwald also referred to Example 5 of the Neudstadt application, which is the same thing as Example 20. Laird at 556: 13-15.

On September 29, 1988, Aventis submitted an Amendment to the '284 application adding the phrase "said compound or salt being substantially free of other isomers" to Claim 24. Def.'s Ex. 38 at A 034383-84.

September 30, 1988 was an eventful day for both Aventis and Schering. First, Aventis filed a Concession of Priority "as to the present broad Count of [the] interference." Pl.'s Ex. 373 at SCH 001453. The Concession indicated that Aventis

> intend[ed] to pursue, in ex parte prosecution, claims directed to a narrower invention, i.e., the compounds of claims 19 to 23 of the involved Teetz application which are substantially free of other isomers, on the basis that this [*69] narrower invention represents a separate patentable invention over the present broad Count of this interference. Further, Teetz [did] not concede priority with regard to this narrower invention.

Id. at 373 at SCH 001453-54. Second, Schering filed a Disclaimer disclaiming Claims 3-6 of the '258 patent. Pl.'s Ex. 314. Third, the license agreement between Schering and Aventis was amended giving Schering a 2.5% royalty for the Schering patents. Pl.'s Ex. 319 at SCH 001484.

On October 12, 1988, the Board of Patent Appeals and Interferences terminated the interference based on Aventis' Concession of Priority.

22. NDA Submitted for Altace

On November 2, 1988, by virtue of the license agreement of the '258 patent with Schering, Aventis submitted a New Drug Application with the FDA for **ALTACE**, Aventis' marketing name for Ramipril. Pl's Ex. 384 at 601. On November 17, 1988, FDA acknowledged receipt of the applications and assigned it NDA No. 19-901. Id. at 635.

23. Aventis' '513 Application

On January 12, 1989, Aventis filed Patent Application No. 07/296,513 (the '513 Application), a continuation of the '284 application. Def.'s Ex. 100 at LUPRAM 000398. [*70] Volker Teetz, Rolf Geiger, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id.

On April 7, 1989, Aventis submitted a Preliminary Amendment to the '513 Application. Id. at LUPRAM 000453. In the amendment, Aventis asked to cancel

Claims 1-18 and add Claims 19-23. Id. at LUPRAM 000455. Claim 19 now included the phrase "substantially free of other isomers." Id.

In addition, to "further support their claim that the claimed compounds are patentable," Aventis attached several declarations stating that Example 20 of the Neustadt Application was not operable, some new and some of which had been submitted with respect to other patents and applications. See id. at LUPRAM 00453-474. One of the declarations submitted on April 7, 1989 was by Dr. Teetz, who stated that Example 20 did not work. Def.'s Ex. 661. Dr. Laird pointed out that, while Dr. Teetz says he repeated Example 20, he doesn't provide the experimental for that repetition. Laird at 503: 2-5. He also made several modifications which are not mentioned in the preamble of his declaration, but are found in the appendix. Laird at 508: 11-14. First, although Example 20 requires one to start with the [*71] compound *cis*, octahydrocyclopentapyrrole, Dr. Teetz started with *cis*, octahydrocyclopentapyrrole hydrochloride. Laird at 503: 9-10. Then, instead of using 10% acetic acid as Example 20 instructs, he changed the amount to 20%. Laird at 505: 6-7. Finally, when he heated the mixture, he only did so for nine hours instead of twenty hours. Laird at 505: 12-13. He ran the experiment for this time even though he stated in his declaration he had followed the procedures outlined in Bonnett's paper, see supra at II.A.5, which instructs heating the mixture under reflux (boiling) for 20 hours. Laird at 513: 5-7.

In addition, after running the experiment, Dr. Teetz reported he got a yield of .05 % of the desired product. Laird at 509: 8. Dr. Laird testified that, although this was a small yield, a person of ordinary skill in the art would not have concluded that the mercuric acetate oxidation process did not work; rather, such a person would conclude it worked but didn't result in a useful yield. Laird at 509: 19. As noted supra, the Court already does not accept Dr. Teetz's credibility based on the fact that he destroyed what he called private notebooks in which he conducted his [*72] repetitions of Example 20. Moreover, since there were no dated notebooks for his company, which presumably was paying for his experiments, the Court does not find such testimony credible. It is easy to understand why Aventis/King would not present Dr. Teetz, their chief witness, by live testimony -- he apparently does not need his notes to testify with particularity exactly what was done twenty-five years before. The Court also **FINDS** that Dr. Teetz's experiment actually resulted in a small amount of Example 20 and thus his declaration does not show that Example 20 does not work. Moreover, the Court **FINDS** that Dr. Teetz's declaration exemplifies behavior by chemists the Court has observed throughout this case, namely, that chemists, especially chemists of high skill such as the chemists involved here, tweak experiments based on their understanding of the literature, their experience, and their goals.

Additionally, Aventis submitted a Declaration from Dr. Becker dated April 29, 1989 in which he concluded that "Compound X," which was Ramipril in the 5(S)-configuration "substantially free of other isomers," was "far superior" to its stereoisomers "as to their ACE inhibiting [*73] activity." Pl.'s Ex. 324 at A 000270. The compounds Dr. Becker compared to Ramipril in the 5(S)-configuration "substantially free of other isomers" included "10 or 11 stereoisomers of [R]amipril, including the four stereoisomers that would result from [E]xample 20 in the Schering patent." Mosberg at 1370: 12-14.

According to Dr. Mosberg, an expert witness for Aventis, "Compound VI," which had the R,R,S,S,S configuration, was the next most potent compound after Ramipril in the 5(S)-configuration "substantially free of other isomers." The R,R,S,S,S configuration was one of the stereoisomers that would result from Example 20. Mosberg at 1371: 25; 1372: 1-13. According to Dr. Mosberg, Ramipril in the 5(S)-configuration "substantially free of other isomers" was "about 18 times more potent" than Ramipril in the R,R,S,S,S configuration. Mosberg at 1373: 6-7. The other stereoisomers tested were even less potent. Mosberg at 1373: 11. Dr. Mosberg also testified that the "only difference [between Ramipril in the 5(S)-configuration "substantially free of other isomers" and Ramipril in the R,R,S,S,S configuration] is the Rs and Ss at the bridgehead" portion of the Ramipril molecule. Mosberg [*74] at 1373: 14-15. Dr. Mosberg concluded that one of ordinary skill in the art would not have expected these results. Mosberg at 1375: 11. While the Court is not convinced that one of ordinary skill in the art would not have expected these results, the Court does **FIND** that Ramipril in the 5(S) configuration is preferred stereoisomer of Ramipril, as it is about 18 times more potent than Ramipril in the R,R,S,S,S configuration.

In addition, Dr. Mosberg explained that an "excipient" in a pharmaceutical compound serves only as

filler and does not add anything to the compound's activity, *i.e.* excipients are therapeutically inactive. Mosberg at 1413: 5-16. He also testified that, when calculating the amount of a drug present in a product, excipients are excluded from the calculation. Mosberg at 1413: 17-20. With respect to adding an isomer that added nothing therapeutically to the drug, however, Dr. Mosberg would not label such an isomer as an "excipient" but as an "impurity." Mosberg at 1414: 2-8. Dr. Mosberg was then asked if there was a difference between the blood pressure lowering ability of a sample containing 10 milligrams of only the 5(S)-isomer of Ramipril and a sample containing [*75] 10 milligrams of the 5(S)-isomer of Ramipril plus 10 milligrams of a therapeutically inactive stereoisomer of Ramipril. Mosberg at 1415: 15-19. Dr. Mosberg testified that he "couldn't say that one would act better than the other to lower blood pressure . . . . if all we're talking about is the therapeutic activity without any regard to possible toxicity or other side effects." Mosberg at 1417: 8-11. Dr. Mosberg said he had no evidence of toxicity or side effects associated with any of the Ramipril isomers. Mosberg at 1417: 12-13. He also said that it was "possible" that a lot of "off-isomer" could "affect absorption," although he had no evidence of that in this context. Mosberg at 1420: 17-25-1421: 4-8. Although the 5(S) configuration of Ramipril is clearly preferred, the Court **FINDS** that no evidence was shown of toxicity or side effects associated with any of the other stereoisomers of Ramipril.

Finally, Dr. Mosberg also testified that, looking at the '722 patent, there was no data indicating that Ramipril in the 5(S)-configuration substantially free of other isomers would lower blood pressure any better than a Ramipril sample with other isomers in it. Mosberg at 1427: [*76] 7-12. When asked "if the advantage of [R]amipril substantially free of other isomers is that it's more potent, wouldn't [he] expect some of that information to make its way into the '722 patent," Dr. Mosberg said he didn't know what would be expected. Mosberg at 1428: 5-18. After reviewing the '722 patent, the Court **FINDS** that there is no data within the patent itself that indicates why the 5(S) configuration "substantially free of other isomers" would be preferred over one not substantially free of other isomers.

23. PTO Office Action

On October 4, 1989, the Examiner rejected claims 19-23 of the '513 patent under 35 U.S.C. 102(g). The Examiner stated:

> Claims 19-23 are rejected as being unpatentable over the lost count of Interference 101,833, under 35 U.S.C. 102(g). In particular, as stated in the judgment rendered Oct. 12, 1988, applicants are "not entitled to a patent containing claims 19-23 corresponding to the count." Although it is applicants' contention that the claims to the specific isomer represent a separate patentable invention over the broad count of the interference (Remarks of April 7, 1989, page [*77] 8), this is inconsistent with the judgment rendered in the interference. The isomers as well as the genus were included in the interference as evidenced by the inclusion of applicants' claims 19-23, drawn to the isomers, as well as both the genus (claim 1) and the specific isomers (claims 2-23) of Gold [the '258 patent] et. al. The term "being substantially free of other isomers" is not considered to be a limitation which distinguishes the instant claims from the claims involved in the interference.

Def.'s Ex. 100 at LUPRAM 000790.

24. Aventis Amends '513 Application

On April 6, 1990, Aventis submitted an Amendment of its '513 Application to the PTO. In its amendment, Aventis maintained that the disclosure in the '258 patent was not prior art to the '513 application and thus the '513 Applicants "need only show that claims 19-23 of the present application are patentable over the lost count of Gold." Id. at LUPRAM 000807-000808. Aventis reasserted its contention that Claims 19-23 were "directed to compounds which are substantially free of other isomers and having five chiral centers in the S-configuration, constitute a separate and patentably distinct invention [*78] from the lost count of Gold et. al." Id. at LUPRAM 000808. Aventis also referred to the Becker Declarations to reargue their position that Claims 19-23 were "unobvious with respect to the isomeric mixtures of the count of Gold et al. by virtue of their unexpectedly superior ACE-inhibiting activity." Id. at

LUPRAM 000810.

25. PTO Action

On June 21, 1990, the Examiner rejected Claims 19-23 of the '513 application under 35 U.S.C. 112 paragraph 1 because "there is no express support for the limitation 'being substantially free of other isomers'" in the specification. Id. at LUPRAM 000855. The Examiner also found that the "working examples do not indicate the exact purity obtained." Id. In addition, the Examiner again rejected the claims as being unpatentable over the lost count of interference 101,833 under 35 U.S.C. 102(g). Id.

26. Aventis' '513 Application

On December 24, 1990, Aventis submitted a Declaration by Dr. Urbach clarifying that the "methods of Example I(1)-I(5) lead only to a single compound in which each of the five chirality centers in the compound has the S-configuration, being substantially [*79] free of other isomers." Id. at LUPRAM 000868. The methods were then examined in greater detail. Id. at LUPRAM 000869-878.

27. Altace Approved by the FDA

On January 28, 1991, Altace under the '258 patent was approved by the FDA to be sold in the United States. Pl's Ex. 384 at 601. The Court **FINDS** that this approval occurred prior to the issuance of the '722 patent, which claims Ramipril "substantially free of other isomers" and which Plaintiff's counsel emphasized is the Altace product.

> The Court: What does substantially free from other isomers do for you?
>
> Mr. Hsing: Is it gives you Altace, this fantastic drug, which is a pure, substantially pure Ramipril. Ramipril *cis endo* 5(S) substantially free from other isomers. That is the Altace product.
>
> The Court: So substantially free from other isomers is absolutely essential for Ramipril?
>
> Mr. Hsing: Yes. . . .

Trans. at 591: 16-24. The Court observes Aventis' emphasis that Altace in the 5(S) configuration is substantially free of other isomers because Aventis' appears to have represented otherwise to the PTO and FDA, as indicated below. See infra II.D. 29, 31.

28. Aventis [*80] Amends '513 Application Again

On February 1, 1991, Aventis submits a Supplemental Amendment to the '513 application, amending claim 24 to correct "an inadvertent error in the structural formula." Id. at LUPRAM 000897. The Amendment also requested the Examiner to consider Dr. Urbach's December 1990 Declaration. Id. at LUPRAM 000898.

29. Application for Extension of '258 Patent Submitted

On March 27, 1991, Aventis submitted, pursuant to 37 C.F.R. § 1.710, a Letter of Transmittal of Application for Extension of the '258 Patent. Pl.'s Ex. 384 at 594. Aventis had the authority to submit this letter because Schering appointed Aventis as agent to submit a patent term extension on its behalf on March 11, 1991. Id. In its letter to the PTO, Aventis stated the following:

> . "Approved product is Ramipril [title of drug and chemical formula provided] . . . . Ramipril is the active ingredient of the new drug, Ramipril capsules, which has received FDA approval." Id. at 596.
>
> . "Ramipril was approved by FDA for commercial marketing . . . on January 28, 1991." Id. at 597.
>
> . "The sole active ingredient of the approved drug (which [*81] is a human drug) is Ramipril as identified above under Paragraph 1 and it has not previously been approved for commercial marketing or use under the [Federal Food, Drug, and Cosmetic Act]." Id.
>
> . "A copy of Statutory Disclaimer under 35 U.S.C. 253(a) filed by Schering Corporation on September 19, 1988 is attached hereto as Exhibit D. Said document disclaims Claims 3 through 6, inclusive, of said Gold et al patent." Id. at

598.

> . "Claim 2 claims a compound according to Claim 1 which is a cis, endo isomer of octahyddrocyclopenta[b]pyrrole-2(s)-carboxylic acid. Claim 2 reads directly on Ramipril . . . ." Id. at 599.

The letter concludes by asking for an extension of 632 days for the '258 patent based on the fact that the product had been subject to a regulatory review period before its commercial marketing. Id. at 604. Neither the original filing with the FDA nor the subsequent extension requested and obtained related to any patent other than the '258 patent.

By licensing the '258 patent from Schering and then requesting an extension of the patent, the Court **FINDS** that Aventis conceded that the '258 patent contained an [*82] enabling disclosure for Ramipril -- to such an extent, in fact, that it sought approval to market Altace from the FDA based on the '258 patent because the '722 patent had not yet been issued. Indeed, in its letter to the PTO for an extension of the '258 patent, Aventis states that "[t]he sole active ingredient" was found in the formula of Ramipril in the '258 patent. Id. at 597. The Court consequently cannot accept any argument from Aventis that, in spite of these actions on its part, the examples provided in the '258 patent did not work and the '258 patent is not prior art. Moreover, since 2000, Schering has made more than $ 48 million by licensing the '258 patent for a 2.5% royalty based on Altace's net sales. McSorley: 1948: 22-25; 1949: 1-15. The Court finds it interesting that Aventis would pay $ 48 million to license a patent yet nevertheless maintain that it was not enabled and is not prior art even though they made applications based on Schering's '258 patent.

Interestingly, in its Post-Trial Brief, Aventis now maintains that the "active ingredient in Altace is [R]amipril substantially free of isomers" in spite of its representation to the PTO that Ramipril under the [*83] '258 patent contained the "sole active ingredient" in Altace. Pl.'s Post-Trial Br. at 30. The Court therefore is tempted to find the '258 patent contained an enabling disclosure for Ramipril "substantially free of other isomers," although, based on the record before it, it is apparent to the Court that the '258 patent disclosed a compound containing Ramipril but not a separated compound of Ramipril in the 5(S) configuration "substantially free of other isomers." [14] The Court can only wonder, though, how Ramipril "substantially free of other isomers" makes any difference given Aventis' representations to the PTO and the FDA that Ramipril not substantially free of other isomers is Altace. Indeed, the Court wonders if Dr. Teetz destroyed his notebooks precisely because he knew Ramipril's purity made no difference, although the Court has no proof to back up its suspicions in this regard one way or the other. The problem for Lupin is that the Court isn't persuaded, by clear and convincing evidence, that Ramipril's isomeric purity doesn't make a difference either. In any event, with all of this said, the Court is not finding that the Ramipril taught in the '258 patent was "substantially [*84] free of other isomers," although it notes that Altace was somehow approved by the FDA based on the '258 patent and prior to the issuance of the '722 patent.

> 14 Indeed, Lupin concedes that the '258 patent describes "a product or substance containing [R]amipril."

30. PTO Action

On April 22, 1991, the Examiner's Interview Summary Record indicates that the Examiner communicated to Aventis that claim 24 of the '513 application "appears to be claiming the same compound free of other isomers as claim 19." Def.'s Ex. 100 at LUPRAM 000899. The Examiner also stated that Aventis agreed to the Examiner's amendment to cancel claim 24. Id.

31. Altace Listed in the FDA Orange Book

In July 1991, Altace is listed in the FDA Orange Book. The Court **FINDS** that this listing occurred prior to the issuance of the '722 patent and was based on the '258 patent. See Pl.'s Ex. 384 at 595-660; Maness at 1665: 3-5.

32. '722 Patent Issues

On October 29, 1991, U.S. Patent No. 5,061,722 issues (the [*85] '722 patent) from the '513 application. Pl.'s Ex. 1. Volker Teetz, Rolf Geiger, Hansjorg Urbach, Reinhard Becker, and Bernward Scholkens are listed as the inventors. Id. It is listed as a continuation of the '284 application, now abandoned, which was a continuation of the '081 application, now abandoned. The '081 application is listed as a continuation-in-part of the '757 application. Id. It is entitled to a foreign priority date of

November 5, 1981 based on Aventis' German Patent Application No. 3143946. The '722 patent is entitled to an effective U.S. filing date of November 3, 1982 based on Aventis' '757 application. The Court notes that the 5(S) configuration apparently was not claimed until October 9, 1984, when PTO noted that Aventis "now claim[ed] the *cis* compound exclusively," see Def.'s Ex. 100 at LUPRAM 000179-80, and that the phrase "substantially free of other isomers" was not introduced with respect to Aventis' patent applications until September 29, 1988 (after the PTO rejected Aventis' patent applications several times). Lupin, however, is not contesting the November 3, 1982 filing date by maintaining that "new material" was added, although, arguably, [*86] it could. The Court **FINDS** that the '722 patent is drawn to Ramipril in the 5(S) configuration "substantially free of other isomers."

33. '258 Patent Term Extension Granted

On December 30, 1991, the PTO extended the term of the '258 patent by 632 days. Pl's Ex. 384 at 662.

34. '944 Patent Issues

On September 20, 1994, Schering's '944 patent issues. Def.'s Exhibit 301. It is a continuation of the '484 application, abandoned, which was a continuation-in-part of the '649 application, now abandoned, which itself was a continuation-in-part of the '886 application, now abandoned. Id. It contains Example 20.

35. The HOPE Study

On January 20, 2000, The New England Journal of Medicine described the results of a study called "The Heart Outcomes Prevention Evaluation Study" ("HOPE Study"). Def.'s Ex. 338. The HOPE Study evaluated the effects of Ramipril in comparison with a placebo in "high-risk" patients having evidence of vascular disease and diabetes but who were not known to have "a low ejection fraction or heart failure." Id. The HOPE Study concluded that Ramipril "significantly reduces the rates of death, myocardial infarction, and stroke" in these [*87] patients. Id. Dr. Pitt, Aventis' expert, testified, by means of deposition testimony read into the record, that the study showed an "overall reduction of 22 percent myocardial infarction and stroke" in patients taking Ramipril compared to those taking a placebo and that Ramipril reduces the risk of cardiovascular death by 25 percent. Pitt at 1783: 3:17. On October 4, 2000, the HOPE indication for Altace was approved by the FDA.

The parties do not dispute that the HOPE Study was an excellent study. The Court **FINDS** that the HOPE Study concluded that Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in high-risk patients who had not had heart failure. The Court also **FINDS** that the HOPE Study compared Ramipril to a placebo, and that the HOPE Study methods were not repeated using ACE-inhibitors in the same patient population. Accordingly, the Court cannot find that Ramipril is superior to other ACE-inhibitors in this regard as there are no studies indicating as such. [15] There was also no evidence provided that the HOPE Study indication resulted from Ramipril being "substantially free of other isomers." The Court therefore cannot make [*88] a finding that Ramipril being "substantially free of other isomers" was the cause of the HOPE Study indication, particularly as the Court has seen no evidence as to the therapeutic value of Ramipril -- or any ACE-inhibitor for that matter -- being "substantially free of other isomers."

15 Perinodopril, an ACE-inhibitor with the 5(S) configuration and a 6, 5 bicyclic ring, apparently also prevented heart attacks. The patients in that study, however, were from a different population. The Court has no direct evidence in this regard, although there was some indication from Dr. Pitt, Aventis' witness, and Dr. Wharton, Lupin's witness, that Perinodopril had a similar indication as Ramipril for preventing heart attacks.

36. '258 Patent Expires

On January 27, 2005, the '258 patent expired.

E. Altace's Commercial Success

The parties stipulated to the following facts in relation to Altace's commercial success:

. In December 1998, King paid over $ 350 million for an exclusive license to sell Altace [*89] in the U.S.

. Wyeth paid King $ 75 million for the right to co-promote Altace in the U.S.

. From 1999-2005, gross sales of Altace in the U.S. were as follows:

- 1999: approximately $ 140.6 million.

- 2000: approximately $ 184.2 million.

- 2001: approximately $ 327.4 million.

- 2002: approximately $ 603.2 million.

- 2003: approximately $ 728.1 million.

- 2004: approximately $ 684.1 million.

- 2005: approximately $ 808.2 million.

. From 1999-2005, net sales of Altace in the U.S. were as follows:

- 1999: approximately $ 121.8 million.

- 2000: approximately $ 161.9 million.

- 2001: approximately $ 284.6 million.

- 2002: approximately $ 450.0 million.

- 2003: approximately $ 536.9 million.

- 2004: approximately $ 347.3 million.

- 2005: approximately $ 554.4 million.

. From 2000-2005, marketing expenses for Altace in the U.S. were as follows:

- 2000: approximately $ 1.5 million.

- 2001: approximately $ 80.4 million.

- 2002: approximately $ 92.7 million.

- 2003: approximately $ 75.3 million.

- 2004: approximately $ 55.1 million.

- 2005: approximately [*90] $ 51.8 million.

In their stipulation, the parties agreed that "net sales = gross sales - customary trade allowance, rebates, discounts and returns." Stipulation of Facts at 2 n.1.

In addition, the Court makes the following findings:

. Between 1991-1999, Altace's market share by total of prescriptions for ACE-inhibitors never exceeded approximately 5.5 percent. Maness at 1679: 14-17.

. Between 1991-1999, the market leaders were Enalapril and Lisinopril based on the number of prescriptions. Maness at 1680: 13-17.

. There is no evidence that doctors proscribe Altace based on its isomeric purity. Wharton at 715.

. At its height, Altace's market share based on number of prescriptions was twelve percent. Maness at 1642: 21-24. From 1999 to 2005, Altace's market share rose from four percent to twelve after the HOPE Study was released and its indication was approved by the FDA. Maness at 1714: 8-14; 1721: 18-23. This increase was the result of an intense marking campaign based on the outcomes of the HOPE study.

. Altace was never marketed on the ground that it is "substantially free of other

isomers."

. Wyeth's co-promotion agreement with King resulted [*91] in King paying Wyeth approximately $ 220 million in 2005. Maness at 1696-97; McSorley at 1951:18-21. Since 2001, as of December 2005, the total promotional fee King has paid Wyeth or is due Wyeth is more than $ 800 million. McSorley at 1951:22-25. This is one-third of King's sales since entering into the agreement in 2000. McSorley at 1952:17-24.

. Since the HOPE Study was released, Schering made more than $ 48 million by licensing the '258 patent for a 2.5% royalty based on Altace's net sales. Wyeth made more than $ 800 million by co-promoting the product. McSorley: 1948:22-1949: 15; 1951:22-1952:7.

III. Conclusions of Law: Validity of the '722 Patent

Because a patent is presumed valid, 35 U.S.C. § 282, 16 the standard of proof for invalidity is higher than the standard of proof for infringement. Unlike the standard of proof for infringement, which is preponderance of the evidence, the party challenging a patent bears the burden of showing invalidity by clear and convincing evidence. Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1339 (Fed. Cir. 2003). Here, Lupin has attacked the validity of the '722 patent by arguing [*92] anticipation, obviousness, and lack of enablement. The Court will address these arguments in turn.

16 35 U.S.C.A. § 282 provides in relevant part:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim . . . .

A. Anticipation

A product or process must be new in order to be patentable. Thus, under 35 U.S.C. § 102, anticipation "requires that there be an identity of invention." Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 619 (Fed. Cir. 1985). A patent is invalid for anticipation -- lack of novelty -- "if a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003). [*93] "A prior art reference may anticipate," however, "without disclosing a feature of the claimed invention if that missing feature is necessarily present, or inherent, in the single anticipating reference." SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343 (Fed. Cir. 2005) (quoting Schering Corp., 339 F.3d at 1377 with approval); see also Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006) ("Anticipation requires a showing that each limitation of a claim is found in a single reference, either expressly or inherently.").

Determining whether something is new requires comparing the claimed product with the products of the relevant prior art. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d. 1313, 1335 (Fed. Cir. 2002). "Prior art," however, "can be an elusive concept because it is not defined in the patent statute, nor is there an all inclusive definition in the case law or literature." HERBERT SCHWARTZ, PATENT LAW AND PRACTICE § 4.I.C (4th ed. 2003). Nevertheless, sections 102(a),(e) and (g) of Title 35 address prior art with respect to novelty, id., and

> [s]ections 102(a) and [*94] (b) operate in tandem to exclude from consideration for patent protection knowledge that is already available to the public. They express a congressional determination that the creation of a monopoly in such information would not only serve no socially useful purpose, but would in fact injure the public by removing existing knowledge from public use.

Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 148, 109 S. Ct. 971, 103 L. Ed. 2d 118 (1989). The relevant sections of 35 U.S.C. § 102 when determining prior art provide:

A person shall be entitled to a patent unless--

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or
>
> . . .
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United [*95] States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language; or
>
> . . .
>
> (g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but [*96] also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Moreover, anticipation requires a prior art disclosure to be "enabling, such that one of ordinary skill in the art could practice the invention without undue experimentation." Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005). While this seems like a straightforward standard in the patent context, it is not, as "[t]he standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112." Id. (citation

omitted).

> While section 112 provides that the specification must enable one skilled in the art to "use" the invention, section 102 makes no such requirement as to an anticipatory disclosure. Significantly, we have stated that anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.

Id. (internal quotations and citations omitted). [*97] Accordingly, when determining anticipation, it is not "necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement." Id. (citing with approval In re Donohue, 766 F.2d 531, 533 (Fed. Cir.1985)).

1. The '258 Patent

Lupin maintains that the '258 Patent qualifies as prior art under 35 U.S.C. § 102(a) and (b) and is enabled. According to Lupin, based on the disclosure of the '258 patent, its claims, and its relationship to the '886 application, one skilled in the art would have been able to prepare, identify, purify and use the 5(S) isomer of Ramipril. Moreover, even if the '258 patent provided for only a mixture of Ramipril isomers, a person of ordinary skill in the art could envisage each member of this limited class of compounds, which would include Ramipril in the 5(S) configuration substantially free of other isomers as found in claim 1 of the '722 patent. Therefore, in Lupin's view, the '258 patent disclosed a small genus that anticipated the species of that genus, namely ramipril in the 5(S) configuration substantially free of other isomers.

Aventis, of course, [*98] disagrees, arguing that a disclosure of a mixture of isomers does not constitute a disclosure of a specific isomer. In Aventis' view, Lupin has not shown that a prior art reference discloses Ramipril substantially free of other isomers and that a mixture containing Ramipril along with several other isomeric versions of Ramipril is insufficient to anticipate. In addition, Aventis maintains that Example 20, the prior art reference Lupin relies on based on the '258 patent's relationship to the '886 application, is not enabled and thus cannot be anticipated. [17] Aventis also argues that Ramipril is one of millions of compounds that falls within the genus of claim 1 of the '258 patent. A genus, according to Aventis, does not anticipate a species.

> 17 As noted supra, the Court refers to Example 20 in this context with the understanding that the '258 patent actually includes the Example in parts and under a different numbering scheme. See supra II.D.16.

Aventis also maintains that the '258 patent is not prior [*99] art because the PTO issued the '258 patent based on the '390 application in which "new matter" that included an example for making Ramipril was added. In addition, according to Aventis, although the "old" matter in the '258 patent originally had a claim to Ramipril (see claim 3), Schering disclaimed this claim, "[telling] the world that it did not invent [R]amipril." Pl.'s Tr. Mem. at 6.

In discussing the '258 patent, the Court begins with the enablement prong as it is the easiest, given that the Court has **FOUND** that Aventis conceded that the '258 patent was enabled when it licensed it from Schering, requested an extension of the patent before the PTO, and relied on it to receive FDA approval for Altace. See supra at II.D.16. The Court has great difficulty finding that the '258 patent was not enabled for the purposes of anticipation under these circumstances. To conclude otherwise, the Court would essentially be finding that Aventis misrepresented the '258 patent's validity before the PTO and the FDA.

Whether the '258 patent constitutes "prior art" for the purposes of anticipation is a much closer question. Fortunately for the Court, however, two arguments made [*100] by Aventis are quickly dispensed with. First, regarding Aventis' disclaimer argument, the Court observes that Aventis provides no legal support for its contention that a disclaimer means that the disclaimee has "told the world that it did not invent" something and thus cannot be considered prior art. Pl's Pre-Trial Br. at 6. The Disclaimer statute is as follows:

> Whenever, without any deceptive intention, a claim of a patent is invalid the remaining claims shall not thereby be rendered invalid. A patentee, whether of the whole or any sectional interest therein, may, on payment of the fee required by law, make disclaimer of any complete claim, stating therein the extent of his

> interest in such patent. Such disclaimer shall be in writing, and recorded in the Patent and Trademark Office; and it shall thereafter be considered as part of the original patent to the extent of the interest possessed by the disclaimant and by those claiming under him.

35 U.S.C. § 253 (emphasis added). MOY'S WALKER ON PATENTS explains:

> Section 253 of the patent statute authorizes the patentee to file two types of disclaimers. The first applies to individual claims [*101] in the patent, and involves the patentee relinquishing all rights under the claim. The second relinquishes a terminal part of the time span of the patent right in the patent as a whole.

MOY'S WALKER ON PATENTS § 3:67 (4th ed. 2005) (emphasis added). As the Court found supra, Schering relinquished claims 3-6 of the '258 patent and licensed the patent to Aventis for a 2.5% royalty to last the life of the patent. The evidence undoubtedly shows that Schering licensed the '258 patent to Aventis precisely because Schering did invent something, namely, a compound that included the Ramipril molecule. See supra II.D.29. Moreover, in exchange for the royalty, Schering relinquished all rights to claims 3-6 of the '258 patent. Indeed, in order to request an extension of the '258 patent, Aventis included in its letter to the PTO that it could act on Schering's behalf precisely because Schering made Aventis its agent with respect to the '258 patent and also had filed a disclaimer. Id. In short, relinquishing rights to a claimed invention -- or as the statute puts it, "stating therein the extent of his interest in such patent" -- is far different from declaring [*102] that one never invented it. The Court is not persuaded by the bald and unsupported assertions Aventis makes otherwise.

With respect to Aventis' "old" versus "new matter" argument, the Court also disagrees. As described in the chronology supra, the '258 patent, on its face, claims priority to the '484 and '886 applications. Based on the '886 application, the Court found that the '258 patent had an effective filing date of October 23, 1980. See supra II.D.3. The Court also found that the first disclosure of Ramipril as part of a mixture that included the 5(S) configuration occurred on October 23, 1980, which is the filing date of the '886 application. The fact that the '390 application, which was filed on July 30, 1984, disclosed "new" material simply does not change the fact that a mixture of Ramipril with the 5(S) configuration was disclosed as part of Example 20 in the October 23, 1980 application. The "new" versus "old" matter argument is a distraction and the Court **FINDS** that the '258 patent is prior art. [18]

> 18 The Court observes that Lupin could question Aventis' November 5, 1981 priority date for the same reasons, as whether that date would encompass "substantially free of other isomers" is suspect, given that the German patent application giving the '722 patent this priority date does not include this phrase or even Ramipril in the 5(S) configuration in isolation. The PTO itself made a point to note that Aventis did not claim the "*cis* compound exclusively" until December 18, 1984. See supra II.D.13.

[*103] The real questions are the following: 1) whether the single prior art reference that is Example 20 disclosed each and every limitation of the claimed invention in the '722 patent; and 2) whether the '258 patent inherently anticipated the 5(S) configuration of Ramipril substantially free of other isomers based on a genus/species relationship between the '258 and '722 patents.

The Court **FINDS** that the '258 patent does not disclose each and every limitation of the '722 patent. The Court has found that the '258 patent, like the '944 patent, includes an enabled example which resulted in a "mixture" of two isomers -- the 5(S) and the S,S,S,S,R -- of Ramipril. See supra II.D.4, II.D.5, and II.D.16. The Court does not find, however, that this prior art reference disclosed Ramipril in the 5(S) configuration "substantially free of other isomers." Consequently, it cannot find that this single prior art reference disclosed each and every limitation of the claimed invention in the '722 patent, namely Ramipril in the 5(S) configuration "substantially free of other isomers." Schering Corp., 339 F.3d at 1377. The limitation "substantially free of other isomers" simply [*104] is not there. Nor was the mixture shown to be one in which the 5(S) configuration was substantially free of the S,S,S,S,R isomer or any other isomer. Therefore, at least in this respect, the Court cannot find anticipation.

The harder question is whether the '258 patent may be considered to be a prior art reference that discloses a

"genus" and thus, if sufficiently small, serves to inherently anticipate a later-named "species." Of course, the fact that a prior art reference discloses a genus does not necessitate the conclusion that all resulting species were inherently disclosed. Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1367 (Fed. Cir. 2004) ("A prior art reference that discloses a genus still does not inherently disclose all species within that broad category."); Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989) ("Under [defendant's] theory, a claim to a genus would inherently disclose all species. We find [this] argument wholly meritless . . . ."); In re Meyer, 599 F.2d 1026 (C.C.P.A. 1979) (declining to find that a disclosed genus anticipated a species because [*105] the "genus, 'alkaline chlorine or bromine solution,' does not identically disclose or describe . . . the species alkali metal hypochlorite, since the genus would include an untold number of species."). Rather, the disclosure of a "small genus may anticipate the species of that genus." Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001) (emphasis added). This is so "even if the species are not themselves recited." Id.; see also Atofina, 441 F.3d at 999 (explaining that "a very small genus can be a disclosure of each species within the genus."). Accordingly, the rule is a narrow one, as finding that a genus anticipates a species requires a court to examine the number of compounds embraced by the genus, the closeness of their relation, and whether the species can be "at once envisaged" from the formula by a person of ordinary skill in the art without having to speculate, combine disclosures not related to each other, or choose indiscriminately from possible combinations. See In re Petering, 301 F.2d 676, 681, 49 C.C.P.A. 993, 1962 Dec. Comm'r Pat. 232 (C.C.P.A. 1962) (holding in a case involving twenty compounds that a general chemical [*106] formula will anticipate a claimed species covered by the formula when the species can be 'at once envisaged' from the formula); In re Ruschig, 343 F.2d 965, 974, 52 C.C.P.A. 1238, 1965 Dec. Comm'r Pat. 482 (C.C.P.A. 1965) (narrowing, in a case involving 130 to 156 very different compounds, Petering's focus by disapproving of "mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them" and "hindsight anticipations"); In re Schaumann, 572 F.2d 312, 316 (C.C.P.A. 1978) (relying on Petering to conclude that claims to a specific compound were anticipated because they "embrace[d] a very limited number of compounds closely related to another" and that the "blood pressure lowering effect of [the compound was] also shared by the class of compounds disclosed by [the genus patent]."); In re Parameswar Sivaramakrishnan, 673 F.2d 1383, 1384-85 (C.C.P.A. 1982) (applying Petering and finding anticipation because one of ordinary skill in the art would not have to "speculate" or "choose judiciously from a genus of possible combinations" to arrive at the claimed invention where a genus disclosed [*107] approximately 70 salts); Metabolite Labs., 370 F.3d at 1367 (upholding a finding of no anticipation where the prior art reference disclosed "no more than a broad genus of potential applications of its discoveries" and that the genus simply invited investigation to discover other uses). [19]

19 To support its inherency argument, Lupin also relies on Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999), which stated:

> . . . when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim. In chemical compounds, a single prior art species within the patent's claimed genus reads on the generic claim and anticipates.

Id. at 1346 (internal citations omitted). The problem with Lupin's reliance on this case is that it involved a species that was patented prior to the genus. The case before the Court here, in contrast, involves a genus patented before an alleged species. As a review of MOY'S WALKER ON PATENTS reveals, whether the genus or the species is patented first changes the analysis. See § 8:13 (noting that, "[s]omewhat more complicated are situations in which the invention at issue is a specie, and the potentially anticipating reference is couched in terms of the genus" and describing a different line of cases addressing the issue).

[*108] To support its genus/species argument, Lupin relies heavily on In re Thomas, 178 F.2d 412, 415-16, 37 C.C.P.A. 754, 1950 Dec. Comm'r Pat. 64 (C.C.P.A. 1949), a case, notably, that has been cited only once since. Thomas involved a composition of insecticides, and the party seeking the patent argued that

the patent claims which related to the "gamma isomer of the compound" were separately patentable from the prior art "mixture of isomers containing a substantial portion thereof." Id. at 413. The Patent Examiner rejected the patent, and the Board of Appeals for the United States Patent Office affirmed. The Court of Customs and Patent Appeals also affirmed the rejection, observing that the "gamma isomer of benzene hexachloride is an old composition" and thus "the state of the prior art was apply sufficient to suggest the use of the gamma isomer as an insecticidal composition." Id. at 415. The appellate court also noted that the insecticidal activity "was due almost entirely to the presence of the gamma isomer." Id. at 414. The appellate court thus affirmed the PTO Examiner's rejection of the patent "as failing to distinguish adequately from the old composition [*109] comprising the crude mixture of all four isomers which are disclosed in the [prior art] patent as a satisfactory insecticide." Id. at 415.

The Court finds Thomas distinguishable for several reasons. First, because it was an appeal of the PTO Examiner's rejection of a patent, the clear and convincing standard that is Lupin's burden here did not apply. Second, unlike the gamma isomer, which was found to be an "old composition," the specific isomer at issue in this case is Ramipril in the 5(S) configuration in essential isolation, which is not an "old composition" found in the prior art. Third, Thomas involved an insecticide -- the toxicity of the compound is precisely its value. The situation before the Court is much different. Although the toxicity of other Ramipril isomers has not been proven one way or the other, it is arguably the absence of toxicity that contributes to Altace's effect. See Mosberg 1311: 15-25 (explaining how small changes cause toxic results). 20 This is probably why more recent decisions dealing with drug compounds reveal that courts are far less inclined to assume that a mixture of isomers makes no difference. See Pfizer Inc. v. Ranbaxy Labs Ltd., 405 F. Supp. 2d 495, 519 (D. Del. 2005) [*110] (finding, in a pharmaceutical case involving the drug Lipitor, that although the genus patent mentioned "calcium as one of the seven listed pharmaceutically acceptable salts," it did not mention the R isomer of "atorvastatin calcium," the species compound claimed in the subsequent patent and thus no anticipation or obviousness); Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W.Va. 2004) (finding, in a pharmaceutical case involving the compound levofloxacin, that a claim to the S isomer of a compound was patentable over a disclosure in the prior art of a mixture having both the R and S isomer of that compound), aff'd 161 Fed. Appx. 944 (Fed. Cir. 2005); In re May, 574 F.2d 1082 (C.C.P.A. 1978) (finding, in a pharmaceutical case involving a pain-relieving drug, that stereoisomers are prima facie obvious but that the prima facie case was rebutted because it was shown that the isomers at issue had different properties and the properties of the drug could not be reliably predicted on the basis of chemical structure). But see In re Adamson, 275 F.2d 952, 47 C.C.P.A. 839, 1960 Dec. Comm'r Pat. 177 (C.C.P.A. 1960) (affirming, in a pharmaceutical case, [*111] the PTO's rejection of a claim for obviousness because a person of ordinary skill in the art would have recognized that the compounds at issue were racemates that could be separated).

> 20 A famous example of a drug having undesirable side effects based on its stereochemistry is Thalidomide. The S-enantiomer of the Thalidomide compound prevented morning sickness. The R-enantiomer of the compound, on the other hand, caused severe birth defects. Mosberg at 31:8-11.

In any event, in applying the genus/species analysis, the Court first **FINDS** that, as the '258 genus embraced two compounds, the S,S,S,S,S version of Ramipril and the S,S,S,S,R version, the number of species included in the '258 patent genus is small. When the example related to Ramipril is followed, the genus does not embrace "billions" or "millions" of possible compounds as Aventis/King so strenuously urged but only two. The Court also **FINDS** that these two compounds are closely related, as they are stereoisomers of the same molecule and have [*112] almost identical configurations. The difficult question is whether the species - specifically the 5(S) configuration in isolation - can be "at once envisaged" from the '258 patent by a person of ordinary skill in the art without having to speculate, combine disclosures not related to each other, or choose indiscriminately from possible combinations.

In this case, the Court has found that the '258 patent specifically encompasses the molecular structure of Ramipril in the 5(S) configuration. What it does not encompass, however, is Ramipril "substantially free of other isomers." While the Court has no doubt that a person of ordinary skill in the art would have been able to envisage Ramipril in the 5(S) configuration, the Court

does have some doubt that a person of ordinary skill in the art would have "envisaged" a substantially pure version of Ramipril in the 5(S) configuration by itself as preferable to a mixture of two Ramipril isomers. Although the Court is not satisfied that Aventis has adequately communicated what "substantially free of other isomers" actually does for Ramipril, Lupin has not shown the Court that the phrase is meaningless either. In fact, Lupin's argument that [*113] the other isomers of Ramipril are inert and thus of no effect mitigate against its contention that someone of ordinary skill in the art would have envisaged Ramipril in the 5(S) configuration substantially free of other isomers. If the other isomers are thought to be inert, why would someone of ordinary skill envision them separately?

Undoubtedly, the Court is disturbed by the fact that Aventis represented to the PTO when it asked for an extension of the '258 patent that the "sole active ingredient" was found in the formula of Ramipril in the '258 patent. Pl.'s Ex. 384 at 597; see supra II.D.29. This suggests that having an isomeric mixture of Ramipril makes no therapeutic difference. On the other hand, the evidence shows that some Ramipril isomers other than the 5(S) configuration have therapeutic potency. See infra II.D.23. The Court thus cannot assume that a mixture of Ramipril with different therapeutic potencies would make no difference as long as the 5(S) configuration predominated the mixture. See Ortho-McNeil, 348 F. Supp. 2d at 729, 763-64 (concluding that a claim to an all-S isomer is patentable over a disclosure containing a mixture of isomers); [*114] May, 574 F.2d at 1090 (holding that a claim to just the R or S isomer was not anticipated by a prior art mixture); In re Schechter, 205 F.2d 185, 191, 40 C.C.P.A. 1009, 1953 Dec. Comm'r Pat. 323 (C.C.P.A. 1953) (unpredictability considered as a factor weighing against a conclusion of obviousness of the claimed compounds). Moreover, Lupin has the heavy burden on this point. Given that everyone seems to agree, including Lupin's experts, that the 5(S) isomer is preferred, the Court is not clearly convinced that a mixture of isomers containing the 5(S) isomer is necessarily equal to a substantially pure compound with the 5(S) isomer. Certainly, the Court is not clearly convinced that one of ordinary skill in the art would have envisaged such, even if such a person knew that the 5(S) configuration of Ramipril had the most potent therapeutic utility out of all of the other possible isomers. The bottom line is that the '722 patent essentially claims Ramipril in the 5(S) configuration in isolation. Although there is some suggestion that Dr. Smith recognized this possibility and perhaps even isolated the 5(S) isomer, there is not enough clear and convincing evidence to persuade this Court to find that [*115] the '722 patent, which is a species, was anticipated by the '258 patent genus. See Pfizer, 405 F. Supp. 2d at 514-15 (in an obviousness analysis, concluding that, although the species patent specifically claimed the active ingredient in the genus patent, there was no infringement).

2. The '944 Patent and the Schering References

Lupin maintains the '944 patent qualifies as prior art under 35 U.S.C. § 102(e) because a person of ordinary skill in the art could readily envision, by means of Example 20 disclosed in the '944 patent's prior art, the compound consisting of the 5(S) configuration of Ramipril. Aventis argues that the '944 Patent is not prior art because Example 20 in the '944 Patent does not work.

The Court **FINDS** that the '944 patent, like the '258 patent, contains an enabled example which resulted in a "mixture" of two isomers - the 5(S) and the S,S,S,S,R - of Ramipril. As noted supra, the Court did not find, however, that this prior art reference disclosed Ramipril in the 5(S) configuration "substantially free of other isomers." Consequently, the analysis applied with respect to anticipation and the '258 patent is [*116] the same. The Court cannot find that this single prior art reference disclosed each and every limitation of the claimed invention in the '722 patent, namely Ramipril in the 5(S) configuration "substantially free of other isomers." Nor can it find that the Schering scientists envisioned Ramipril in the 5(S) configuration "substantially free of other isomers." Accordingly, the Court **FINDS** that the 5(S) configuration of Ramipril substantially free of other isomers in the '722 patent was not anticipated by the '944 patent and the Schering References leading up to it.

3. Sample SCH 31925

Lupin maintains that Dr. Smith's physical preparation of sample SCH 31925 qualifies as prior art under 35 U.S.C. § 102(g), maintaining that "United States does not permit the first person to file a patent application to receive patent rights if someone else in the United States invented the subject matter first." Lupin also argues that, because Aventis/King has not limited its claims to only the pure 5(S) isomer, Dr. Smith was not obligated to make her 5(S) isomer pure to show prior invention. Moreover, according to Lupin, the proper

analysis turns on whether Dr. Smith [*117] actually conceived the invention's structure and an operative method of making it.

Aventis/King contends that SCH 31925 fails to anticipate because, as it is a mixture, it does not meet every element of the claimed invention, emphasizing that Dr. Smith never separated the mixture into its individual component isomers. Aventis/King also argues that SCH 31925 is not a prior art reference because Lupin failed to show that Dr. Smith had a contemporaneous appreciation of what isomers were in the SCH 31925 sample. Finally, Aventis/King maintains that SCH 31925 is not prior art because non-public laboratory work does not qualify as prior art if it is "abandoned, suppressed, or concealed."

"Section 102(g) operates to ensure that a patent is awarded only to the 'first' inventor in law." Apotex U.S.A. Inc. v. Merck & Co., Inc., 254 F.3d 1031, 1035 (Fed. Cir. 2001). In addition to determining priority in interference proceedings, § 102(g) may also be asserted as a defense to an infringement suit. Id. In such an instance, the party asserting the defense must present, by clear and convincing evidence, that the invention was made by another, prior, inventor. Id. at 1037-38. [*118] Thus a "patent may be invalid as anticipated due to the prior conception and reduction to practice by another of the patentee's invention." Texas Instruments v. United States ITC, 988 F.2d 1165, 1177 (Fed. Cir. 1993).

In this case, there is no question that Dr. Smith prepared a substance in SCH 31925 that contained the 5(S) configuration of Ramipril and that this sample was based on Example 20 provided in the '886 application. See supra at II.D.3 and 4. The problem is that SCH 31925 was a mixture and not Ramipril in the 5(S) configuration substantially free of isomers. Accordingly, as with the '258 patent and the '944 patent, the Court cannot find by clear and convincing evidence that SCH 31925 is a prior art reference disclosing Ramipril in the 5(S) configuration substantially free of other isomers. The Court also cannot find by clear and convincing evidence that Dr. Smith conceived of the 5(S) isomer separate and apart from the S,S,S,S,R isomer that was part of the SCH 31925 mixture. As noted supra, she certainly envisioned the 5(S) isomer, just as she "contemplate[d] all possible isomers." See II.D.2 (quoting Smith at 766:16-767:2. What [*119] Lupin has not shown by clear and convincing evidence, however, is that she envisioned the 5(S) configuration of Ramipril "substantially free of other isomers" in its essential isolation. She also never committed to narrowing down the compound to one isomer. Although she did comment that "it was hoped that it would be narrowed down," this narrowing could have included two or three isomers. Id. Thus the Court cannot **FIND** by clear and convincing evidence that Dr. Smith conceived of Ramipril in the 5(S) configuration substantially free of other isomers. Clear and convincing evidence is much stronger than preponderance of the evidence. One may apply while the other may not.

B. Obviousness

An invention must be nonobvious to a person of ordinary skill in the art in order to receive patent protection. In re Kahn, 441 F.3d 977, 985 (Fed. Cir. 2006). Under 35 U.S.C. § 103(a),

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as [*120] a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

When determining whether an invention would have been obvious, the legal question is this: are the differences between the subject matter sought to be patented and the prior art such that the subject matter as a whole would have been obvious at the time of the invention to a person having ordinary skill in the art? Kahn, 441 F.3d at 985. "Obviousness may not be established using hindsight." Kahn v. GMC, 135 F.3d 1472, 1479 (Fed. Cir 1998), cert. denied, 525 U.S. 875, 119 S. Ct. 177, 142 L. Ed. 2d 144 (1998). In addition, when determining obviousness, "the invention must be considered as a whole and the claims must be considered in their entirety." Id. at 1479-80.

As established by Graham v. John Deere Co., 383 U.S. 1, 17, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), in order to reach the legal question of obviousness, a court is required to make the following factual determinations: 1) the scope and content of the prior [*121] art; 2) the differences between the prior art and the claims at issue;

and, 3) the level of ordinary skill in the pertinent art. See also Ruiz v. A.B. Chance Co., 234 F.3d 654, 663 (Fed. Cir. 2000) (stating "[o]ur precedent clearly establishes that the district court must make Graham findings before invalidating a patent for obviousness."). In addition, in order to avoid applying hindsight, a court must weigh "secondary considerations of nonobviousness." Id. at 662, 667. Secondary considerations of nonobviousness "include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." Id. at 662-63.

With respect to chemical compounds, however, a prima facie case of obviousness is established when there is "structural similarity between claimed and prior art subject matter [and] where the prior art gives reason or motivation to make the claimed compositions." Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)). "[A] reasonable expectation of success, not absolute [*122] predictability" supports a conclusion of obviousness." Id. Thus, Lupin must prove: 1) that the prior art would motivate a person of ordinary skill in the art to make Ramipril in the 5(S) configuration substantially free of other isomers, and 2) that the prior art "reasonably suggest[s] that the compound would exhibit its unique combination of properties." Ortho-McNeil, 348 F. Supp. 2d at 749.

While this is the general standard for chemical compounds, Lupin maintains that the Court of Appeals for the Federal Circuit has held that stereoisomers are prima facie obvious and therefore the analysis apparently ends. In Dillon, the appellate court indeed stated:

> [I]f an examiner considers that he has found prior art close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a prima facie case of obviousness. The burden then shifts to the applicant, who then can present arguments and/or data to show that what appears to be obvious, is not in fact that, [*123] when the invention is looked at as a whole.

919 F.2d at 696 (internal citations omitted). Moreover, in Jones, the Court of Appeals for the Federal Circuit enumerated the categories of structural chemical similarity that have given rise to prima facie obviousness, and one of these categories is stereoisomers. In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992) (listing In re May, 574 F.2d 1082 (C.C.P.A. 1978) as standing for this proposition). However, in its more recent decision in In re Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997), the Federal Circuit applied the Graham factors to an isomeric compound. Ortho-McNeil, 348 F. Supp.2d at 749 n.19. Therefore, while it appears that stereoisomers may be prima facie obvious, there is no per se rule. Thus, even when stereoisomers are involved, a court must be careful "[t]o prevent the distortions of hindsight" and pay "close attention to the supposed reason or motivation for making the claimed compound is critical." Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 2001 U.S. Dist. LEXIS 18361, 2001 WL 1397304, *5 (S.D. Ind. 2001). As CHISUM ON PATENTS [*124] explains,

> Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Further, many such new compounds are obvious in the sense that any competent chemist could have synthesized them if requested or motivated to do so.

2 DONALD S. CHISUM, CHISUM ON PATENTS § 5.04 (2000) [hereinafter "CHISUM ON PATENTS"] (cited in Eli Lilly, 2001 U.S. Dist. LEXIS 18361, 2001 WL 1397304, *5). Accordingly, even with chemical compounds, when finding motivation or suggestion, "there should be a reasonable likelihood that the claimed invention would have the properties disclosed by the prior art teachings [and thus these findings] should be made with a complete understanding of the first three 'Graham factors.'" Id. [21]

> 21 If prima facie obviousness is found, the patent owner may rebut the finding by offering evidence of unexpected results. Dillon, 919 F.2d at 692-93. "Rebuttal may take the form of 'a comparison of test data showing that the claimed compositions possess unexpectedly improved properties . . . that the prior art does not have, that the prior art is so deficient that there is no

> motivation to make what might otherwise appear to be obvious changes, or any other argument . . . that is pertinent." Mayne, 104 F.3d at 1342 (quoting Dillon, 919 F.2d at 692-93). Because the Court does not find that separating the stereoisomers in this case was prima facie obvious, rebuttal on this point was not necessary.

[*125] **1. The Scope and Content of the Prior Art**

As the findings of fact indicate, the prior art includes the Schering references, the '258 patent, Dr. Smith's work and the teachings involving Captopril, Enalapril, snake venom from the Brazilian viper, and other ACE-inhibitors.

2. One of Ordinary Skill in the Art

Obviousness turns on "the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). In this way, a court must distinguish between the actual inventor's skill and the skill of a person of ordinary skill in the art. Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985).

> The actual inventor's skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something-call it what you will-which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 [*126] by inquiring into what patentees (i.e., inventors) would have known or would likely have done, faced with the revelations of references.

Id. Accordingly, "[a] person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights . . . ." Id.

As found supra, a person of ordinary skill in the art in this case would be someone with a Ph.D. in chemistry or organic chemistry with knowledge of stereochemistry, or have a similar amount of training in association with preparing chemical compounds in the pharmaceutical industry. Such a person would be familiar with stereochemistry and with methods for preparing, isolating, and characterizing pharmaceutical compounds. For the purposes of this obviousness analysis, such a person is not an innovator who conducts expensive, systemic research or is given to extraordinary insights.

3. Differences between the Prior Art and the Claims at Issue--Prima Facie Obviousness

Lupin argues that Ramipril in the 5(S) configuration substantially free [*127] of other isomers is prima facie obvious in view of the Schering references as well as prior art disclosures related to Merck's Enalapril. Aventis/King maintains that Example 20, if it worked, discloses a mixture of compounds and that nothing in the prior art would have motivated someone to select a compound having all of its chiral carbons in the S-configuration.

The Court has little problem finding that the structural similarity between the diastereomeric mixture Dr. Smith created -- the S,S,S,S,S isomer and the S,S,S,S,R isomer -- and Ramipril in the 5(S) configuration substantially free of other isomers are similar. Not only are the chemical building blocks the same, but the chiral carbons are almost identical. The questions are whether the prior art "gives reason or motivation to make the claimed compositions," namely Ramipril in the 5(S) configuration substantially free of other isomers, and whether the prior art would reasonably suggest that the compound would exhibit its unique combination of properties.

Lupin fails to persuade this Court by clear and convincing evidence on the first question, whether the prior art would motivate someone of ordinary skill in the art to [*128] make Ramipril in the 5(S) configuration substantially free of other isomers. Lupin argues that the Schering references teach an overwhelming preference for (S) and single isomers. Specifically, Lupin maintains that the '944 patent taught a preference for the all-(S) isomer by itself, as it includes a statement that the isomers of the Examples should be isolated. Def.'s Ex. 301, col. 15, lines 10-15; col. 10, lines 28-41. Moreover, according to Lupin, additional teachings outside of the Schering references would direct a person of skill in the

art to a single all-(S) isomer, not one that is part of a mixture. These teachings include: the fact that the snake venom of the Brazilian viper, Captopril, and Enalapril are all-(S) single isomer compounds; that Merck's publication of Enalapril's structure in Nature taught that, if the all-(S) configuration in Enalapril was not followed, "significant potency was lost . . . about a 700-fold difference," see id. at II.D.1; that Merck stated in their published papers that the stereochemistry had important design implications for the synthesis of other inhibitors; that Merck reported it obtained high, if not entire, purity for its all-(S) [*129] isomer; and that ACE-inhibitors are amino acid derivatives, all of which, except for one (cystine) have the S-configuration.

In response, Aventis/King maintains that the (S) configuration in the chiral centers in snake venom, Captopril, and Enalapril occur in the "side chain" portion of the Ramipril molecule. The Ramipril molecule is distinct from these compounds in that it includes the 5,5 bicyclic ring, which created the "bridgehead" portion of the Ramipril molecule not present in the snake venom, Captopril or Enalapril. As for the '944 patent teaching a preference for the all-(S) isomer by itself, Aventis/King points out that Lupin is relying on a part of the '944 patent description of a 6, 5 compound instead of the 5,5 compound at issue in this case. Finally, Aventis/King argues that only hindsight allows Lupin to assert that Ramipril's other isomers are inactive. When the '722 patent was issued, according to Aventis/King, "it was not known that the other isomers were inactive" and thus "one skill in the art would not have known that the other isomers conferred no medical benefit." Pl.'s Post-Trial Br. at 24-25.

Although it is very a close question, given that the standard is [*130] clear and convincing evidence, the Court **FINDS** that a person of ordinary skill in the art would not by clear and convincing evidence have necessarily been motivated to isolate Ramipril in the 5(S) configuration substantially free of other isomers. First, the Court is not persuaded by clear and convincing evidence that the snake venom, Captopril, and Enalapril would have motived a person of ordinary skill in the art to combine the teachings in the Schering references and/or the '944 patent to arrive at (S) isomers in the bridgehead portion of the Ramipril molecule. The experts in this case agree that the snake venom, Captopril, Enalapril, and the Nature article discussing Enalapril do not describe the bicyclic configuration found in the bridgehead portion. Ganem at 367: 18-25; 368: 1-25; Mosberg at 1319: 9-12; 1321: 24-25; 1322: 1-15; 1490: 11-14. Moreover, Dr. Smith testified that neither Captopril nor Enalapril provided any information on the bridgehead atom's stereochemistry. Smith at 953: 5-15. While in hindsight it seems obvious that Ramipril would likewise be in the all-S configuration, the Court must be wary of that temptation given that bridgehead portion of the Ramipril [*131] molecule does not replicate any structure in the snake venom, Captopril, or Enalapril. The Court observes that another ACE-inhibitor, Trandolapril, which, unlike Captopril or Enalapril, has a bridgehead, has an S and an R in the two chiral centers of the bridgehead. Mosberg at 1325: 3-7. Finally, even if it was obvious that the preferred isomer of Ramipril would be in 5(S), that does not necessitate the conclusion that the 5(S) version should be as free from other isomers as possible. The Court **FINDS** that the prior art does not by clear and convincing evidence show that a person of ordinary skill in the art would be motivated to make Ramipril in the 5(S) configuration substantially free of other isomers. It is the isolation of the 5(S) isomer from a mixture of Ramipril isomers that gives the Court the most concern, especially in light of the difference between the preponderance of the evidence and the clear and convincing evidence standards.

The Court is also not persuaded by clear and convincing evidence that the '944 patent taught a preference for the 5(S) isomer by itself either. The '944 patent states: "When diastereomeric products result from the synthetic procedures, [*132] the diastereomeric products can be separated by conventional chromatographic or fractional crystallization methods." Def.'s Ex. 301, col. 15, lines 10-15; col. 10, lines 28-41. What this indicates to the Court is that, if a diastereomer is made, it may be separated. There is no suggestion, however, that it should be separated or that its separation necessarily results in the all-S isomer. Finally, as Aventis/King points out, this portion of the patent is referring to a 6, 5 compound having a "cis, syn" configuration and not a 5,5 compound, which is Ramipril. If the standard was preponderance of the evidence, the Court might determine that a person of ordinary skill in the art would apply the same configuration from one ring-structure to another. That is not the standard, however, and, even if the Court found as much, the problem of isolating the 5(S) configuration remains. In other words, regardless of what the 6, 5 ring system taught to a person of ordinary skill in the art, the '944

patent does not clearly motivate that person to create a substantially pure isomeric version of Ramipril.

The Court also agrees with Aventis/King that the evidence shows that, as of 1981, [*133] there was no expectation that Ramipril substantially free of other isomers would be more or less potent than a mixture. While it is clear that the 5(S) configuration is preferred, it simply is not clear that this preference related to the 5(S) configuration being separate from other isomers. As the Finding of Facts indicate, nor was this separation particularly easy to do. Put another way, having other isomers in the mixture did not seem to be of great concern to the Schering scientists -- indeed, it did not seem to be of great concern to the Aventis scientists until they could not get their own patent approved. Accordingly, the Court is not persuaded by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to isolate Ramipril in the 5(S) configuration substantially free of other isomers. [22]

22 Because the Court finds there was no motivation for a person of ordinary skill in the art to separate the mixture, it is not necessary for the Court address whether the prior art would "reasonably suggest" that "the compound would exhibit its unique combination of properties." See Ortho-McNeil, 348 F. Supp.2d at 749.

[*134] With respect to secondary considerations, which must be weighed even though the Court is not persuaded by clear and convincing evidence on the motivation element, the Court is not convinced that the evidence establishes that the invention of Ramipril in the 5(S) configuration was not obvious. First, with respect to Aventis/King's argument that Altace is a commercial success, the Court **FINDS** that there is no evidence linking the fact that Ramipril is "substantially free of other isomers" to Altace's success. A "nexus must be established between the merits of the claimed invention and evidence of commercial success before that evidence may become relevant to the issue of obviousness." Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1324 (Fed. Cir. 2004) (citation omitted). Aventis/King has shown no nexus whatsoever between Altace's success and the drug being "substantially free of other isomers." Instead, Aventis/King's argument seems to be that, because "substantially free of other isomers" is in the '722 patent, any commercial success that Altace had is per se related to this attribute. This is hard for the Court to accept, however, when [*135] Aventis/King admits that Altace was approved by the FDA and manufactured under the '258 patent, which included the compound Ramipril not substantially free of other isomers. The Court, as it has said several times, is not convinced one way or the other that "substantially free of other isomers" accomplishes anything. It certainly has no evidence that Altace's isomeric purity -- a unique characteristic of Ramipril, according to Aventis/King -- is connected in any way to Altace's commercial success. In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996) (stating that commercial success is "relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention").

There is substantial evidence that Altace became commercially successful as a result of an intensive marketing campaign based on the HOPE Study. This is not to say that the HOPE Study is invalid. Indeed, it appears to be a very good study with a good outcome for Altace. What is apparent, however, is that the HOPE Study was heavily marketed to the medical community by means of a mighty sales force and sales consequently rose as a result [*136] of an expensive outlay. [23] See supra II.F. (findings related to Aventis/King's marketing efforts). Moreover, given that, from 1998 to 2005, Altace was protected by the '258 patent as well as the '722 patent and market entry by others was therefore precluded, the inference of non-obviousness because of commercial success is weak and the Court finds it non-existent. Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005) (finding weak commercial success when patents kept other competitors from the market). "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." Id. at 1376. When an idea cannot be brought to market sooner because a patent stands in the way, the rationale for finding commercial success becomes much less. Id.

23 The world is replete with examples of advertising and the effects of it, and the situation before the Court here is no different. Mr. Hill, the famous CEO advertiser, increased Lucky Strikes' sales by 38% in six weeks with his phrase "Lucky Strike Green has Gone to War." In Freakonomics, the authors similarly describe how Listerine dramatically increased its sales by essentially

inventing halitosis. STEVEN D. LEVITT & STEPHEN J. DUBNER, FREAKONOMICS (HarperCollins 2005).

[*137] Second, with respect to the secondary consideration of "long-felt need," there is little question that there were several effective ACE-inhibitors on the market before Altace entered the market. See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 884 (Fed. Cir. 1998) (explaining that whether an invention fulfilled a long-felt need is evidence of nonobviousness). There was simply no "long-felt need" for another ACE-inhibitor. As the cross-examination of Dr. Scholkens pointed out, Enalapril and Ramipril are equipotent when administered intraduodenally. See supra II.D.3. As for the HOPE Study indication, the Court is not convinced that Altace performs better than other ACE-inhibitors in preventing heart attacks in high-risk patients because the HOPE Study tested Altace against a placebo. See supra II.E. Enalapril, for example, whose potency was equal to Ramipril's when administered intraduodenally, apparently has not yet been tested for this result. The other drugs studied and cited by Aventis/King were tested on different populations. Moreover, there is nothing in the '722 patent related to preventing heart attacks in high-risk [*138] patients. Ortho-McNeil, 348 F.Supp.2d 713, 758 (N.D.W.Va.2004) ("Evidence of the existence of a long-felt need may be found, among other places, in the prior art, . . . or in the patent itself."). Consequently, the Court is simply not persuaded that Altace is meeting a "long-felt" need.

As for copying, there is no question that Lupin attempted to copy Altace. That is what generic drug companies do. That is why their products are cheaper. As MOY'S WALKER ON PATENTS observes, however, "[the copying] rationale is considerably weakened . . . by the fact that there are various other reasons why an invention may have been copied." § 9:60 (4th ed. 2005). In this case, the reason why Lupin attempted to copy Altace is because the ANDA process allows a generic drug company to challenge a drug patent by alleging the patent is invalid. Aventis Pharma Deutschland GMBH v. Lupin Ltd., 403 F. Supp.2d 484, 486 (E.D. Va. 2005) (explaining the "paragraph IV" provision and the ANDA process). Accordingly, given that there is a statute in place that encourages generic drug companies to challenge patents, Aventis/King's copying argument is weak.

Finally, the Court is [*139] not persuaded that the evidence shows that Altace indicates "unexpected results." For example, Dr. Scholken's indication that Ramipril substantially free of other isomers had an ACE-inhibiting activity of about three times greater than Enalapril resulted from the drugs being given to dogs after intravenous injection. See II.D.13. Although not included in his Declaration before the PTO, however, Dr. Scholkens testified in this case that Ramipril and Enalapril were "approximately equipotent" after intraduodenal administration. Id. When asked why he did not include this information in his Declaration before the PTO, Dr. Scholkens stated "the declaration is not a scientific paper." The Court thus has some doubt that Ramipril substantially free of other isomers was as "far superior" to Enalapril as Dr. Scholkens suggested, as he withheld certain information because his declaration was not a "scientific paper." [24] Thus, what he maintains is a "scientific conclusion" is not a "scientific paper." In addition, although there is no question that the 5(S) isomer of Ramipril is preferred, there is some question as to whether it is preferred in isolation as opposed to a mixture. [*140] The Court has said many times it has found no evidence to support a conclusion one way or the other. This open question as to the value of Ramipril being "substantially free of other isomers" causes the Court to question Aventis/King's claims of "unexpected results."

24 This merely emphasizes the need for cross-examination of paid advocates.

Finally, the HOPE Study indicated, unquestionably, that Altace was found to prevent heart attacks, strokes, and diabetes. As the Court has noted, however, the drug was not tested against other drugs -- it was tested against a placebo. Nor did the tests include Enalapril, which was equipotent in the high-blood pressure context. This is perhaps why the American College of Cardiology does not single out Altace in its guidelines regarding the treatment of chronic stable coronary disease. Wharton at 723: 12-16; Def.'s Ex. 610. If there is no clinical indication designating Altace over any other ACE-inhibitor for this purpose, the Court has a difficult time concluding that the [*141] HOPE Study indicated unexpected results by being substantially free of other isomers.

C. Enablement/Lack of Written Description

"[T]o be enabling, the specification of a patent must

teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Under 35 U.S.C. § 112, P1,

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

When determining enablement, "[t]he specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1334 (Fed. Cir. 2003). [*142]

Lupin's first argument with respect to enablement essentially rests upon asking this Court to apply the same standards of enablement to the Schering References as it would to the '722 patent. See Def.'s Trial Br. at 33. In other words, if the Court had found that the '944 and '258 patents were not enabled for the reasons Aventis/King urged, then the same reasons should be applied to the '722 patent. Given that the Court has found that Schering References and the '258 patent were enabled, Lupin's concerns in this regard have been addressed.

Lupin goes on to maintain that the specification of the '722 patent provides no guidance as to when a compound qualifies as being "substantially free of other isomers." Def.'s Opening Tr. Br. at 7. The problem with Lupin's argument is that it has urged, throughout this case, that it would have been obvious to one of ordinary skill in the art to separate Ramipril isomers until the 5(S) configuration was accomplished. Thus the Court has a difficult time accepting the argument that a person of ordinary skill in the art would not be enabled, without undue experimentation, to make Ramipril in the 5(S) configuration substantially free of other isomers. [*143]

Lupin makes a good point that "substantially free of other isomers" is easily defined legally, as the Court did in its Claim Construction Order, but much harder to define scientifically. In other words, the Court has indeed wondered, throughout this case, what "substantially free of other isomers" actually accomplishes for Ramipril. The problem is that this question of whether a portion of the invention matters has nothing to do with whether a patent is enabled -- it is a question of indefiniteness. While Aventis/King has not convinced this Court that "substantially free of other isomers" makes a bit of difference, Lupin did not convince this Court that the phrase is fatally indefinite either, as the Court found that "'substantially free of other isomers' is not indefinite given its plain-meaning and the fact that it would indicate to a person of ordinary skill in the art that the compound was largely free of other isomers but not 100% pure." See Claim Construction Order at 24-26.

Finally, the fact that the Court found that Lupin's Ramipril capsules with up to 0.50% of Isomer-1 infringed the '722 patent under the doctrine of equivalents does not change this Court's view in regards [*144] to any of its rulings. When it found infringement based on the doctrine of equivalents, the Court, indeed, concluded that it is Ramipril -- the active ingredient -- that mattered under that analysis. The problem for Lupin now is that Aventis/King has effectively raised enough questions in this Court's mind about whether the purity of Ramipril in the 5(S) configuration also matters. This is a different question from whether Lupin's version of Ramipril was essentially the same as Aventis' Altace. If the preponderance of the evidence standard was the standard to judge this case, the Court might agree with Lupin, but, as the Court has said many times, that is not the standard to be applied here since the '722 patent was granted. A patent is presumed valid and invalidity must be shown by clear and convincing evidence.

IV. Conclusion

Obviously, although the Court is finding for Aventis/King, it has reservations in doing so. Using common sense, and not the intricacies of patent law, the bottom line is that Altace is going to be on the market for approximately two years longer than it probably should be because it was first approved under the '258 patent, which has expired. [25] [*145] But the Court applies the law -- not necessarily common sense.

25 Indeed, Aventis/King does not dispute that

Altace -- the Altace they have been selling all along -- was first approved under the '258 patent.

> The Court: You know, Mr. Katcoff, [attorney for Aventis], something worries me about this entire matter. And what really gave me some concern is you were manufacturing Altace. Under the '258 patent. . . Isn't that correct?
>
> Mr. Katcoff: We were manufacturing --
>
> The Court: Is that correct?
>
> Mr. Katcoff: Under the '258 patent, absolutely correct. But the '258 patent is a different story. It is not prior art. Not prior art.

See Closing Arguments Trans. at 33-34.

In the Court's view, this case involves a circumstance that is not adequately addressed by the ordinary validity tests of anticipation, obviousness, and enablement. No factor under any of these tests allows the Court to consider the fact that the very same product appears to have been approved and made first under [*146] one patent and then later under another patent. But evaluating the patents outside of the products approved by the FDA and the products manufactured under them results in an outcome that effectively allows one product -- Altace -- to have approximately two more years of patent protection than it probably should have.

In addition, although inequitable conduct might have occurred, the Court is very much aware that Aventis/King may simply be taking advantage of happenstance. Clearly, Aventis fought hard to make and produce Altace and, to cover its bases, both licensed the '258 patent from Schering and simultaneously pursued its own patent. There is nothing inequitable or wrong about doing that. As soon as it received a license from Schering, it went to the FDA for the approval of Altace. If it had received the '722 patent first, it undoubtedly would have gone to the FDA for approval using that patent. The fact, however, that the '722 patent was approved subsequently to the '258 patent has allowed Aventis to maintain, at this point in time, that Altace falls under the '722 patent and not the '258 patent. When Aventis was pursuing the '722 patent in the 1980s and early 90s, there [*147] is no evidence that it intended this result. Rather, the timeline that resulted from Aventis' efforts now works in its favor. Considering the high standard of clear and convincing evidence required to set aside the '722 patent, Lupin's effort fails and the '722 patent remains in effect and is therefore valid in so far as this case is concerned.

With that said, the Court must observe that Aventis' arguments with respect to the '258 patent in this matter are plainly inconsistent with its representations to the PTO and FDA. There is no question that Aventis, after licensing the '258 patent from Schering, obtained FDA approval to market Ramipril using the trade name Altace and that it also obtained an extension of the '258 patent from the PTO representing that the '258 patent covered "the sole active ingredient" in Altace. This is what gives the Court concern. The problem for the Court is that it has been persuaded that there is no proof of clear and convincing evidence that the '722 patent is invalid. The other problem is that inconsistency and clever lawyering do not necessarily constitute misrepresentation on the part of the inventors.

In addition, while Aventis points out that there [*148] are several drugs where both the species and genus are listed in the FDA's Orange Book, the Court wonders whether these species and genuses were listed simultaneously or, as is the case here, at different times. 26 More importantly, this seems to be an FDA problem rather than a PTO problem. Or, more specifically, it seems to be a problem with the Hatch-Waxman ANDA process, as the simple filing of a patent in the Orange Book puts an entire patent litigation process in motion. In other words, if it is common for species and genera to be listed at different times yet cover the same drug, then drug manufacturers may indeed use the Orange Book to protect that drug from competition -- they are essentially extending patent protection by means of the FDA and not the PTO. Solving these policy problems, however, is not the Court's role but the role of Congress.

> 26 Plaintiff King pointed out in closing arguments that, in Pfizer Inc. v. Ranbaxy Labs Ltd., 405 F. Supp.2d 495 (D. Del. 2005), the district court concluded that the species was patentable over the genus and noted that both the species and genus have different expiration dates. It is unclear to this Court, however, if both the

genus and species were listed in the Orange Book and when.

[*149] Indeed, the anomaly presented by this case is that Lupin may not manufacture the Ramipril that Aventis licensed with the FDA under the '258 patent, even though that patent has expired, because of the doctrine of equivalents as applied with respect to the '722 patent. Aventis candidly indicates that they applied for FDA approval under the '258 patent to manufacture and market Ramipril substantially free of other isomers as the '722 patent had not yet been granted. Thus from technical and clever maneuvering Aventis has lengthened its monopoly to the detriment of the public. In reality, the '722 patent should not under these circumstances be any longer than the '258 patent -- in other words, both patents should have expired at the same time. Clearly, the pharmaceutical lobbyists have won this round.

Finally, even though no one appears to know (or be able to admit) whether Ramipril "substantially free of other isomers" makes any therapeutic difference, the fact is that open question raises enough doubt in the Court's mind for it to be unable to find for Lupin under the clear and convincing evidence standard. The '722 patent unquestionably patents Ramipril as a compound in an essentially [*150] pure molecular form, namely in the 5(S) configuration "substantially free of other isomers." The '258 patent unquestionably does not, and Lupin has not shown, by clear and convincing evidence, that the purity of Ramipril -- the essential isolation of Ramipril in the 5(S) configuration -- was anticipated or obvious. It is quite possible that the '722 patent should have never been granted, but once it was granted, attacking its validity is a very difficult task indeed. Unfortunately, the law is the law.

The Court **FINDS** for the Plaintiffs. Accordingly,

. The Court **FINDS** that Lupin has failed to prove, by clear and convincing evidence, that the '722 patent is invalid;

. The Court **DECLARES** that making, using, selling, offering to sell, and/or importing the Ramipril capsules described in Lupin's ANDA application constitutes infringement of the '722 patent;

. The Court **ENJOINS** Lupin, its officers, agents, servants and employees from making, using, offering to sell, selling, or importing the Ramipril capsules described in its ANDA application until the expiration of the '722 patent; and

. The Court **ORDERS** that the effective date of the [*151] products described in Lupin's ANDA application shall not precede the expiration of the '722 patent. [27]

The Clerk is **DIRECTED** to send by facsimile and United States mail a copy of this Order to all counsel of record.

27 Under 35 U.S.C. § 271(e)(4), the remedies available to a plaintiff that successfully protects its patent in ANDA cases are:

> (A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
>
> (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product, and
>
> (C) damages or other monetary relief may be awarded against an infringer only if there has been commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug or veterinary biological product.

[*152] **IT IS SO ORDERED.**

Robert G. Doumar

UNITED STATES DISTRICT JUDGE

Norfolk, Virginia

July 17, 2006

EXHIBIT 2

ELI LILLY AND COMPANY, Plaintiff, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and INTERNEURON PHARMACEUTICALS, INC., Involuntary Plaintiffs, vs. TEVA PHARMACEUTICALS USA, INC., Defendant.

IP 02-0512-C-B/S

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF INDIANA, INDIANAPOLIS DIVISION

2004 U.S. Dist. LEXIS 14724

July 29, 2004, Decided

SUBSEQUENT HISTORY: Affirmed by **Eli Lilly & Co. v. Teva Pharms. USA, Inc., 2005 U.S. App. LEXIS 14583 (Fed. Cir., July 13, 2005)**

PRIOR HISTORY: Eli Lilly & Co. v. Teva Pharms. USA, Inc., 2003 U.S. Dist. LEXIS 13069 (S.D. Ind., July 21, 2003)

DISPOSITION: Patent was found valid and enforceable.

COUNSEL: {*1} For Eli Lilly and Company, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Dominick A Conde, Fitzpatrick Cella Harper & Scinto, New York, NY USA.

For Massachusetts Instit of Tech, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Jeffrey C McDermott, Krieg Devault Alexander Capehart, Indianapolis, IN USA. Timothy J Vezeau, Katten Muchin Zavis Rosenman, Chicago, IL USA.
For Interneuron Pharmaceuticals Inc, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Jeffrey C McDermott, Krieg Devault Alexander Capehart, Indianapolis, IN USA. Timothy J Vezeau, Katten Muchin Zavis Rosenman, Chicago, IL USA. Brian H Corcoran, Katten Muchin Zavis Rosenman, Washington, DC USA.
For Teva Pharmaceuticals USA Inc, DEFENDANT: David O Tittle, Bingham McHale, LLP, Indianapolis, IN USA. Steven J Lee, Kenyon & Kenyon, New York, NY USA.

JUDGES: SARAH EVANS BARKER, JUDGE, United States District Judge.

OPINION BY: SARAH EVANS BARKER

OPINION:
FINDINGS OF FACT AND CONCLUSIONS OF LAW

This case comes before the court, after a bench trial held November 12-24, 2003, for decision on the issue of patent invalidity under 35 U.S.C. §§ 102 {*2} and103. Plaintiff, Eli Lilly and Company ("Lilly"), filed suit against Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), for infringement of U.S. **Patent No. 4,971,998** ("the **'998 patent**"). Teva conceded, based on the court's July 21, 2003 Claim Construction ruling, that its generic drug indication infringed Claim 2 of the **'998 patent**. Therefore, the only decision currently before the court is whether the **'998 patent** is invalid, either as anticipated under **35 U.S.C. § 102** or obvious under **35 U.S.C. § 103**. For the reasons explicated below, we conclude that the **'998 patent** was neither anticipated nor obvious, and is, therefore, valid and enforceable.

Findings of Fact

I. Background n1

- - -Footnotes- - -1

n1 Unless otherwise indicated, these background facts are taken from the parties' joint submission of Facts That Are Admitted and Will Require No Proof at Trial. (Dkt. # 167.)

- - -End Footnotes- - -

Plaintiff Eli Lilly and Company ("Lilly") is a corporation organized and existing under {*3} the laws of the State of Indiana, having its principal place of business in Indianapolis, Indiana. Lilly is engaged in the business of research, development, and commercialization of pharmaceutical drugs. (See Tollefson Tr. p. 883). Involuntary plaintiff Massachusetts Institute of Technology ("MIT") is a university located in Cambridge, Massachusetts. Involuntary plaintiff Interneuron Pharmaceuticals, Inc. ("Interneuron") is a Delaware corporation having its principal place of business in Lexington, Massachusetts. Interneuron is now known as Indevus Pharmaceuticals, Inc. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware, having its administrative offices in North Wales,

Pennsylvania, and a principal place of business in Selleville, Pennsylvania. Teva is engaged in the generic manufacture of pharmaceutical drugs.

This patent infringement action arises under 35 U.S.C. §§ 271(e) and281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and1338(a). Venue is proper under 28 U.S.C. §§ 1391(c) and1400(b).

II. {*4} Trial Witnesses

A. Lilly's trial witnesses:. Dr. Richard Wurtman, a co-inventor of the **'998 patent**, is the Cecil H. Green Distinguished Professor in the Department of Brain and Cognitive Science at MIT. (R. Wurtman Tr. pp. 6-7, 11). He holds an M.D. from Harvard University and also trained at the National Institutes of Health. (R. Wurtman Tr. p. 7). Dr. Wurtman has published about 1000 articles relating to his research, which focuses on neurotransmitters and their effect on the brain and behavior. (R. Wurtman Tr. p. 12).

. Dr. Judith Wurtman, the other co-inventor of the **'998 patent**, directs a program in women's studies at the Clinical Research Center at MIT, and is also the founder and director of a private weight loss center in the Boston area. (J. Wurtman Tr. p. 157). She holds a Ph.D. in cell biology from George Washington University, and also did post-doctoral work in nutritional biochemistry at MIT. (J. Wurtman Tr. pp. 158-59).

. Dr. Gary Tollefson is Vice-President of Lilly's Research Laboratories, and holds an undergraduate degree in Psychology, an M.D., and a Ph.D. in Psychopharmacology, all from the University of Minnesota. (Tollefson {*5} Tr. p. 880). Dr. Tollefson was previously Chairman of the Department of Psychiatry at St. Paul Ramsey Medical Center, and Associate Professor, Department of Psychiatry, University of Minnesota. (Tollefson Tr. p. 881). He joined Lilly in 1991, and later held the position of fluoxetine team leader, responsible for the development of Sarafem(R). (Tollefson Tr. pp. 881-82).

. Dr. Jean Endicott is Professor of Clinical Psychology at the College of Physicians and Surgeons, Columbia University, Department of Psychiatry, and the Director of the Premenstrual Evaluation Unit at Columbia Presbyterian Medical Center. Dr. Endicott is also the Chief of the Department of Research Assessment and Training at the New York State Psychiatric Institute. (Endicott Tr. p. 1043). Dr. Endicott has a Ph.D. in Clinical Psychology from Columbia University, but is not a medical doctor. (PTX 5, Ex. A.) Dr. Endicott has authored, or co-authored, more than fifty publications regarding PMS (Endicott Tr. pp. 1045-46), and has more than twenty years of experience in the treatment of women suffering from PMS, including designing and executing clinical trials since 1982. (Endicott Tr. pp. 1043-44). Dr. Endicott {*6} has served on the Editorial Board of the numerous publications. (Endicott Tr. pp. 1046-47). She has also been a consultant and member of several prestigious professional committees including the Task Force on Nomenclature and Statistics of the American Psychiatric Association for DSM-III and DSM-III-R, which was responsible for deriving the definition of Late Luteal Phase Dysphoric Disorder ("LLPDD") in 1987. (Endicott Tr. p. 1045). As well, she was a member of the "LLPDD/PMDD" Work Group DSM-IV which in 1994 derived the definition of PMDD. (Endicott Tr. pp. 1045-46).

. Dr. Lynda Smirz is an Obstetrician/Gynecologist in private practice at the Women's Health Alliance in Indianapolis, Indiana. (Smirz Tr. p. 1296). She has over 20 years of experience in obstetrics and gynecology. (Smirz Tr. p. 1296-97). Dr. Smirz also served as a Clinical Assistant Professor, Department of Obstetrics and Gynecology, Indiana University School of Medicine. (Smirz Tr. p. 1297). Dr. Smirz sees patients regularly and is familiar with the key scientific literature relating to the standard of care among Obstetricians and Gynecologists for the treatment of PMS as of October 1987. (Smirz Tr. pp. 1298-1300). {*7}

. Dr. Pierre Blier is Professor, Departments of Psychiatry and Neuroscience at the University of Florida. (Blier Tr. p. 1348). Dr. Blier began his research on serotonin in 1978. (Blier Tr. p. 1349). He holds a Master's and a Ph.D. in Neuroscience, and an M.D., all from the Universite de Montreal. Dr. Blier also completed a post-doctoral fellowship in the neuropharmacology of serotonin at Laboratoires d'Etude et de Recherche Synthelabo in Paris. Dr. Blier currently serves on the numerous Editorial Boards and is an Editor for the *Journal of Psychiatry and Neuroscience*. (Blier Tr. p. 1350). Dr. Blier has authored or co-authored 170 peer-reviewed publications; he also consults extensively with pharmaceutical firms. (Blier Tr. p. 1349).

. Dr. Daniel Smith is the Clare W. Barker Chair and Professor of Marketing, and Associate Dean of Academics at the Kelley School of Business, Indiana University, Bloomington, Indiana. (Smith Tr. p. 942). Dr. Smith has over 15 years of experience in Marketing, with an emphasis on brand and product line management. (Smith 942:25-943:9).

. Mr. Michael Tate is Managing Director of InteCap, Inc., an international business consulting {*8} firm that focuses on intellectual property matters in the

context of litigation, valuation and licensing. (Tate 1211:9-17). Mr. Tate has over 15 years of experience in business consulting, which has included serving as a consultant and expert witness in a wide range of litigation matters. These matters involved analysis and evaluation of financial and accounting data for the purpose of determining the extent of economic damages as well as the valuation of various intellectual property rights and the determination of reasonable royalty rates. (Tate Tr. pp. 1211-12).

B. Teva's trial witnesses:. Dr. Laura Miller is Associate Head of the Department of Psychiatry, Chief of the UIC Women's Mental Health Program, and an Associate Professor of Psychiatry at University of Illinois at Chicago ("UIC"). Her responsibilities include designing and implementing clinical and teaching programs related to women's mental health. (DTX VN, ZE; Miller Tr. p. 204.) Dr. Miller has never, however, been involved with a clinical trial relating to PMS. (Miller Tr. p. 373.) Dr. Miller graduated from Harvard Medical School in 1982 and completed her psychiatry residency at the University of Chicago {*9} from 1983-86. (DTX VN, ZE.) Though, as of October 1987, Dr. Miller was not board certified (DTX ZE) and had not prescribed any agents to women suffering from LLPDD (Miller 375:12-19), she has since become a board-certified psychiatrist and developed particular expertise in the treatment of women's reproductive-related mental illness, including premenstrual mood disturbances. (DTX VN, ZE; Miller Tr. pp. 204-5.) The use of fenfluramine, which is not a psychotropic drug, to treat eating disorders is outside her area of expertise. (Miller Tr. pp. 502-03). She has authored or co-authored numerous articles, given talks or discussions at university or professional forums and taught graduate level and continuing medical education classes related to psychiatric conditions in women, including those related to the menstrual cycle. (DTX ZE.) She published her first article on PMS in 2000. (Miller Tr. pp. 372-73). In addition, Dr. Miller was asked by both the American Psychiatric Association and Continuing Medical Education Incorporated to write their review articles on premenstrual mood disorders. (DTX ZE.)

. Dr. Andrea Rapkin is a Professor in the Department of Obstetrics and Gynecology {*10} ("OB/GYN") of the UCLA Medical Center. (DTX VO; Rapkin Tr. p. 541-42.) Dr. Rapkin graduated from medical school in 1979, and finished her OB/GYN residency in 1983. (Id.) Dr. Rapkin has been a principal investigator on approximately thirty clinical studies and has published over thirty research papers. She is a reviewer for the major OB/GYN journals. (Rapkin Tr. pp. 542-43.) Dr. Rapkin is also the lead author of the prior art reference entitled "Whole Blood Serotonin in Premenstrual Syndrome," which was published in the journal "Obstetrics and Gynecology." (DTX FF; Rapkin Tr. p. 544.)

. Dr. Walter Brown is a Clinical Professor of Psychiatry at the Brown University School of Medicine and at the Tufts University School of Medicine. Dr. Brown has been on the faculty at Brown University since 1974. Prior to joining the faculty of Brown University, he held academic appointments at the Mount Sinai School of Medicine in New York and at the Yale University School of Medicine in Connecticut. (DTX VL, ZG; Brown Tr. p. 651.) Dr. Brown received an M.D. from Duke University in 1967, and completed his residency at the Yale University Department of Psychiatry from July 1968 through June {*11} 1969, and from July 1971 through June 1972. He held fellowship positions at the National Institute of Child Health and Human Development/National Institutes of Health in Bethesda, Maryland, from July 1969 through June 1971, and at Yale University from July 1972 through June 1974. (DTX VL, ZG.) Dr. Brown has been a practicing psychiatrist and has conducted clinical research in the area of psychiatry for about thirty years. (Brown Tr. p. 651.) Dr. Brown has been a principal investigator in over 100 clinical trials, including trials relating to the drug fluoxetine. (DTX VL, ZG; Brown Tr. pp. 651, 653.) Dr. Brown has co-authored several articles relating to the use of fluoxetine in the treatment of PMS, the first in 1990. (DTX VL, ZG, GJ; Brown Tr. p. 651; 653-54.)

. Dr. Sanford Bolton is an expert in biostatistics. (DTX VK, ZF; Bolton Tr. p. 833.) He received his Ph.D. in Pharmacy from the University of Wisconsin in 1958, and his Masters in Biostatistics from Columbia University in 1966. (Id.) Over his forty-year career in biostatistics, he has published numerous articles in the field and is the author of the treatise entitled "Statistics in Clinical Studies and Pharmaceutical {*12} Processes." (Id.)

. Mr. George Gould is an expert in pharmaceutical licensing. (DTX VM, XR; Gould Tr. p. 1001.) He received a B.A. in Organic Chemistry in 1958 from Johns Hopkins University, a J.D. in 1963 from Columbia University School of Law, and a LL.M. in 1973 from New York University Law School. (DTX VM, XR.) Mr. Gould has over thirty years of licensing experience in the pharmaceutical industry. Among other things, Mr. Gould was vice-president of licensing and corporate development and chief patent counsel at

an international pharmaceutical company, Hoffmann-La Roche Inc. (DTX VM, XR; Gould Tr. p. 1002-3.) Over the course of his career, Mr. Gould has negotiated several hundred licenses in the pharmaceutical field for large pharmaceutical as well as start-up biotech companies. (Id.)

. Dr. David Schmittlein is a marketing expert. He is currently the Ira A. Lipman Professor, Professor of Marketing and the Deputy Dean and Chief Academic Officer of the Wharton School of the University of Pennsylvania. His twenty-three years at the Wharton School have been spent teaching, consulting and conducting research in the field of marketing. (DTX VP, YE; Schmittlein {*13} pp. 1247-48.) Dr. Schmittlein received a bachelor's degree in Mathematics from Brown University and a Ph.D. in Business from Columbia University in 1980. (DTX VP, YE; Schmittlein Tr. p. 1248.) Dr. Schmittlein has authored over forty research publications, which have been published in the major journals in marketing, statistics and economics. (DTX VP, YE; Schmittlein Tr. p. 1249.)

III. Prozac(R) n2--Lilly's Development of Fluoxetine

- - -Footnotes- - -2

n2 We respect that Prozac, like the other pharmaceutical brand names used in this Entry, is a registered trademark. Therefore, we acknowledge the trademark upon our first use of each brand name. Thereafter, however, so as not to add to an already detailed Entry, we omit the trademark symbols.

- - -End Footnotes- - -

Fluoxetine belongs to a class of compounds called selective serotonin reuptake inhibitors ("SSRIs"). (Dkt. # 167). During the 1970s and 1980s, Lilly researched, developed and tested the drug fluoxetine. (See, e.g., DTX A, WY). In 1977, Lilly was issued **U.S. Patent No. 4,018,895** {*14} ("the **'895 patent**") entitled "Aryloxyphenylpropylamines in Treating Depression." (DTX A cover page.) The **'895 patent** claimed a method of treating humans suffering from depression with a daily dosage of 1 to 200 mg of fluoxetine. (DTX A, col. 18, l. 1-2; col. 17, l. 28-30.) The **'895 patent** also mentions the usefulness of fluoxetine in treating disorders of sleep, sexual performance, appetite, muscular function and pituitary function; however, it does not mention PMS or the treatment thereof. (Miller Tr. pp. 437-38; DTX A col. 14, ll. 17-22; Endicott Tr. pp. 1059-60).

Then, in 1986, Lilly was issued **U.S. Patent No. 4,590,213** ("the 213 patent") entitled "Anti-Anxiety Method." (DTX WY cover page). The '213 patent claims a method for treating anxiety in humans, both men and women, in need of such treatment with the daily administration of 20-80 mg of fluoxetine. (DTX WY col. 1, l. 52-56; col. 2. 34-35.) Although the '213 patent adds schizophrenia and hypothermia to the list of disorders treatable with fluoxetine in the **'895 patent**, the '213 patent, like the **'895 patent**, does not mention PMS. (Miller Tr. pp. 437-39; Endicott Tr. pp. 1061-63).

As part of the research and development of {*15} fluoxetine, Lilly conducted numerous clinical trials, which established the efficacy of fluoxetine in the treatment of major depressive disorder. In March 1985, Paul Stark, the inventor of the '213 patent, and C. David Hardison, a Lilly employee, published a study, *A Review of Multicenter Controlled Studies of Fluoxetine vs. Imipramine and Placebo in Outpatients with Major Depressive Disorder*, 46 J. Clin. Psychiatry 53-58 (1985) (the "Stark reference"), which determined that fluoxetine relieved the symptoms of depression equally as well as another antidepressant, impramine, and significantly better than placebo, with fewer and less severe side effects than impramine. (DTX GB pp. 53, 57)

Stark intended to test a hypothesis that a deficiency of serotonin caused affective disorders, including depression. He stated, "According to one serotonin hypothesis of depression, reduced serotonin function is manifested in depressive symptoms. Thus, a compound [like fluoxetine] that selectively inhibits the reuptake of serotonin, enhancing serotonin function, should ameliorate the symptoms of depression." (Id. p. 53.) Among Stark's patients were men and women. Some of these women likely {*16} would have been premenopausal; however, Stark did not diagnose any of them with PMS. Such a diagnosis was not necessary given the purpose of Stark's study, which was to treat depression, not PMS. Although Stark spoke of treating the symptoms of depression, he never suggested the use of fluoxetine to treat PMS. (See Miller Tr. pp. 433-34).

Also in March 1985, J.B. Cohn and Charles Wilcox published a study comparing the efficacy and safety of fluoxetine with those of imipramine and placebo. *A Comparison of Fluoxetine, Imipramine, and Placebo in Patients with Major Depressive Disorder*, 46 J. Clin. Psychiatry 26-31 (1985) (the "Cohn reference"). Like Stark, Cohn posited that "fluoxetine's specific inhibition of serotonin reuptake by the neuron suggest that this compound might be an effective antidepressant." Again, Cohn found that "fluoxetine

relieved the symptoms of depression better than placebo and with fewer and less severe side effects . than imipramine." (DTX AV pp. 28-29, 31.) Cohn, too, treated outpatients with major depressive illness, a class that presumably would have included both men and women of varying ages. He did not diagnose any of the women with PMS or even {*17} mention PMS, thereby demonstrating that he had no intent to treat the syndrome. (See Miller Tr. pp. 435-36).

The PTO examiner did not consider either the Stark reference or the Cohn reference during the prosecution of the applications that led to the issuance of the '998 patent. (DTX K, M, N.) However, the Stark and Cohn references lend further support to the claims of the '895 and '213 patents. They neither teach away from the patented inventions nor extend the serotonin hypothesis to PMS.

In addition to clinical trials like those conducted by Stark and Cohn, Lilly conducted large-scale clinical trials of fluoxetine in order to gain FDA approval to market the drug ("Fluoxetine Trials"). (Dk. # 167, P19; see also Bolton Tr. p. 836.) The records of these clinical trials were confidential, and as such, were not known to anyone outside of Lilly, including the Wurtmans or the examiner of the '998 patent. Lilly and the clinical investigators conducting the trials were required to maintain the confidentiality of these records. (DTX MW at P 104 3236)

A number of the pre-October 1986 Fluoxetine Trials had an "open label" arm where both the patient and the physician knew whether {*18} the patient was being treated with fluoxetine. (DTX AV at 26, MP, Brown Tr. p. 653.) During these open-label trials, fluoxetine was administered to, among others, at least 112 women between the ages of 18 and 45 who were diagnosed with major depressive disorder. This diagnosis did not include PMS specifically as these trials were not intended to test the efficacy of fluoxetine as a PMS therapy. PMS requires a careful diagnosis, which must be charted over several menstrual cycles in order to avoid the retrospective misallocation of mood changes to the menstrual cycle. (See Rapkin Tr. pp. 593, 596-97; Brown Tr. pp. 783-84, 787; Bolton Tr. 864-65; Endicott Tr. pp. 1063, 1066; PTX 206 at 1539; PTX 205 at 46; DTX FR p. 390). These 112 women with major depressive disorder were administered fluoxetine in daily dosages between 5 mg to 120 mg over a period of at least thirty days. (D-DEM O; DTX XC; Bolton Tr. p. 843.)

As part of Teva's anticipation claim, Teva engaged Dr. Bolton, a statistical expert, to calculate the probability that one or more of these 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS. Dr. Bolton {*19} used the binomial equation to calculate the probability of a specific event occurring where there are two possible outcomes, *i.e.*, the woman has a disturbance of mood and/or appetite associated with PMS or does not have such a disturbance. (Bolton Tr. pp. 845-46; D-DEM P.) In performing his calculations, Dr. Bolton assumed the prevalence rate of premenstrual depression among these women to be 65 percent, a rate taken from the expert report of Dr. Miller. n3 (Bolton Tr. p. 851; 865-66.) With this prevalence rate, Dr. Bolton calculated the probability that one or more of the 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS to be greater than 99.99999 percent. (Bolton 852:7-852:16; D-DEM W). Lilly challenges the 65 percent prevalence rate used by Dr. Bolton because it measures a lifetime, not a concurrent, possibility that the two disorders will co-occur. (DTX FR at 390.) Dr. Bolton, however, responded that even if the prevalence rate of premenstrual depression among women who suffer from depressive disorders was as low as 10 percent, the probability that at least one of the 112 women had PMS would be 99.99925 {*20} percent. (Bolton Tr. pp. 853-54; D-DEM Y.)

- - -Footnotes- - -3

n3 Dr. Miller testified that the prevalence rate of premenstrual depression among women who suffer from depressive disorders has been estimated in several studies to be approximately 65 percent. (See, e.g., DTX FR (June 1987) at 390; Miller Tr. pp. 232-33.)

- - -End Footnotes- - -

Dr. Bolton, of course, speaks in probabilities. He could not identify any one patient record and say with certainty that a female subject actually had PMS. (Bolton Tr. p. 871). Moreover, as stated above, none of the clinical trial participants, which included both men and women, were actually diagnosed with PMS. They were not diagnosed with PMS because in that context it was irrelevant; the purpose of the Prozac clinical trials was to determine the effectiveness of fluoxetine in treating depression, not PMS. (Brown Tr. pp. 783-84; Bolton Tr. pp. 864-65, 868-69; Endicott Tr. pp. 1063-65). To address this criticism of Dr. Bolton's analysis, Teva asked another of its experts, Dr. Brown, to examine the patient record {*21} for one of the 112 women in Dr. Bolton's sample. A patient record is a document used by clinical researchers to record all of the information gathered on a single research subject during a clinical trial. (Brown Tr. p. 686). The patient

record was of a 37-year old woman with major depressive disorder ("the patient") who participated in a fluoxetine clinical trial in 1982. (DTX LD; Brown Tr. pp. 688-89.) At the beginning of the trial, the patient was asked from what other illnesses or conditions did she suffer. She indicated that she had hay fever, but did not mention PMS. (Endicott Tr. pp. 1064-65; DTX LD at P 58 730). In the normal course, however, Dr. Endicott testified that, if the patient suffered from PMS, she would have mentioned it. (Endicott Tr. pp. 1141-43, 1143-45).

The patient was in the double-blind portion of the study for the first eight weeks. (See Brown Tr. p. 709; DTX LD at PZ 58 727-PZ 58 800.) The patient began the open-label phase of the study one month after the completion of the double-blind study. The open-label phase lasted for six to seven months. The patient record indicated that for most of the open-label phase the patient was given 60 mg of fluoxetine {*22} daily, while at the end of the open-label phase, the daily dosage of fluoxetine was 20 mg. (Brown Tr. pp. 709-11, 726.)

The patient record for week 5 stated that the patient experienced "premenstrual tension," which the patient record explains as "premenstrual problems of tension and irritability." The patient also reported that she "felt worse last week. She said she always feels more depressed [and] tense before her menstrual periods." (Brown Tr. pp. 704-05; DTX LD at PZ 58 768, PZ 58 772.) At the patient's next visit, which was week 6, she reported that "premenstrual tension [was] very much less last week than usually experienced." (DTX LD at PZ 58 780; Brown Tr. pp. 705-06.) The patient record also contains results of the Hamilton Psychiatric Rating Scale for Depression, which measures the severity of depression. (Brown Tr. p. 689.) The patient's Hamilton Depression Rating decreased from 12 in week 5 to 7 in week 6. Dr. Brown testified that this decrease is consistent with the patient having experienced premenstrual tension during week 5 which was relieved by week 6. (Brown Tr. p. 706.)

In spite of the anecdotal comments in the patient record relied on by Dr. Brown, the patient {*23} record simply does not supply sufficient information to make a PMS diagnosis. (Endicott Tr. pp. 1065-66). For example, as Dr. Brown did not (and could not have) interviewed the patient, we have no information concerning the date of the onset of menses; similarly, we do not have any evidence of daily ratings or documentation that she had the PMS before she was diagnosed with major depression. (Id. pp. 1145-46; see also Brown Tr. p. 785). Many women attribute the occurrence of their symptoms to the menstrual cycle, but when carefully examined, those women do not actually have PMS. (Endicott Tr. p. 1066). Dr. Brown conceded that "when thoroughly evaluated, the overwhelming majority of women who say they have PMS do not in fact have disabling symptoms related specifically to the menstrual cycle." (Brown Tr. p. 787; PTX 211 at 570).

An accurate diagnosis of PMS requires daily prospective ratings, taken over two months, in order to show whether symptoms onset during the luteal phase and remit during the follicular phase, which is the hallmark of PMS. (Rapkin Tr. pp. 593, 596-97; Endicott Tr. p. 1066; PTX 206 p. 1539; PTX 205 at 46). Dr. Miller admitted that charting is the most {*24} accurate, but not the only, way to diagnose PMS, and Dr. Brown stated that the "acid test for PMS is prospective ratings." (Miller Tr. p. 383, 386; Brown Tr. p. 787; PTX 199 p. 55; PTX 211 p. 570). Two months of ratings are used in order to rule out the possibility that in any one month the symptoms could have been caused by some other issue such as problems at work, unpaid bills, or other life stresses. (Rapkin Tr. p. 597; Endicott Tr. p. 1066). Dr. Brown admitted that there were no reports of PMS rating scales in the patient record he reviewed. (Brown Tr. p. 788). Thus, in the absence of daily ratings, a patient's self report is insufficient to make an accurate diagnosis of PMS. (Endicott Tr. p. 1066).

Relying only on a patient's recollection can lead to misdiagnosis, especially when the patient suffers from PMS and major depressive disorder. (Rapkin Tr. 593-96; Endicott Tr. p. 1066, 1145-46, PTX 205 p. 46). Dr. Endicott testified that it is very difficult to diagnose PMS in a woman who has major depressive disorder. (Endicott Tr. pp. 1066-67). They share symptoms, and one needs to carefully examine the patient to ensure that the symptoms onset during the luteal phase and offset {*25} during the follicular phase. (Id. p. 1067).

All of the 112 patients in Dr. Bolton's sample were taking fluoxetine during the open label phase of the clinical trial. The evidence is less clear as to whether the patient was taking fluoxetine during the blinded portion, during which she complained of premenstrual tension. Lilly never produced the protocol for this study. Lilly did, however, release protocols for other clinical trials. Those protocols indicate that a patient could not receive fluoxetine during the open-label phase of a clinical trial unless the patient had received fluoxetine during the double-blind phase and had substantially improved during the double-blind phase and exhibited a clinically significant response, or that patient had received a drug other than fluoxetine and not exhibited a clinically significant response. (DTX NB at PZ 6 1560, MZ at PZ 6 2260, MU at PZ 918 1121, MP at PZ 6 1566, MY at PZ 6 1557.)

Because this individual patient was on fluoxetine in the open-label portion and had substantially improved during the double-blind phase, we conclude that she was on fluoxetine during the double-blind portion. (See Brown Tr. pp. 722-23.) This reasoning {*26} is supported by her Hamilton Depression Ratings, which substantially improved over four weeks, a result consistent with the patient taking fluoxetine. (See Brown Tr. p. 703.) In addition, the patient lost weight, which was also consistent with fluoxetine effects. (Brown Tr. pp. 689, 705-06, 707-08, 711; Miller Tr. p. 263). However, one inconsistency: if the patient was being treated with fluoxetine at the time of her comment, then one would expect (based on what we now know) that given the rapid action of fluoxetine in relieving PMS symptoms, she would not have any PMS symptoms in Week 5 because she would have been administered fluoxetine for at least one week prior to her comments. (Endicott Tr. pp. 1068-69, 1146-47). Therefore, we conclude that the patient, while likely given fluoxetine to treat her major depression, did not have PMS.

The patent examiner did not consider the Fluoxetine Trials during prosecution of the applications that led to the issuance of the **'998 patent**. (DTX M, N.) In an August 4, 1988 office action during prosecution of U.S. Patent Application Ser. No. 111,771, the first application in the series from which the **'998 patent** issued, the patent examiner rejected {*27} the pending claims, which included methods of treatment using the drug d-fenfluramine. One of the bases of the patent examiner's rejection was that the prior use of d-fenfluramine in clinical work would have inherently anticipated the pending claims:

All of the clinical work with [d-fenfluramine] has clearly involved treating a large number of women of menstruating age with this compound. Given the common occurrence of PMS among such women the claimed method would have to inherently haven't [sic] been practiced in one or more of the patients used in the study. In addition, if this drug is now a commonly prescribed drug this would provide further evidence that it would have inherently (if unintentionally) been used in carrying out claimed process.

(DTX M at 137, Office Action, U.S. App. Ser. 07/111,771, dated Aug. 4, 1988 at 5.) In the same office action, the patent examiner requested more information from the Wurtmans and MIT: "In evaluating the merits of the above prior art rejection it would be helpful to know approximately what percentage of menstruating women regularly experience PMS. If applicants have knowledge on this question they are requested to make it {*28} of record with their response to this office action." (DTX M at 138, Office Action, U.S. App. Ser. 07/111,771, dated Aug. 4, 1988 at 6.)

First, we disagree with the patent examiner that the Fluoxetine Trials would have been relevant. Not only did they not demonstrate an intent to treat PMS, but as shown above, without a specific diagnosis of PMS, it would have been impossible to tell whether the claimed method had been inherently practiced. In addition, although some studies indicate that the prevalence rate of PMS among women with major depression is approximately 65 percent, as shown above, that number reflects a lifetime, not concurrent, prevalence rate. Most importantly, assuming *arguendo* that these records would have been relevant, the Wurtmans would not have had access to these Fluoxetine Trial records at the time of the filing of the **'998 patent**. The clinical records were the confidential property of Lilly. (DTX MW p. P 104 3236).

On September 6, 1983, Lilly filed a New Drug Application ("NDA"), No. 18-936, with the FDA, seeking approval to market fluoxetine for major depressive disorder. The FDA approved Lilly's NDA on December 29, 1987. Lilly was the exclusive marketer {*29} of fluoxetine in the U.S. from January 1988, when Prozac came on the market, through August 2001, when the Federal Circuit declared invalid the last of Lilly's fluoxetine-related patents. (Dkt. # 167, **Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955 (Fed. Cir. 2001).**) Prozac was one of the best-selling drugs in the world, having achieved over a billion dollars in sales. (See Smith Tr. p. 984.)

IV. The '998 patent

In the mid-to-late 1970's, the Wurtmans, inventors of the **'998 patent**, developed a theory that the food individuals consume affects brain serotonin. (R. Wurtman Tr. pp. 17-18). To test this theory scientifically, they conducted animal studies to determine if the administration of drugs known to increase serotonin, in particular fenfluramine and fluoxetine, would cause a reduction in carbohydrate consumption. (Id. pp. 18-19.). From these studies, they concluded that fenfluramine and fluoxetine caused the animals to eat less carbohydrate in proportion to protein, and also to consume fewer calories. (R. Wurtman Tr. pp. 19-20; J. Wurtman Tr. pp. 159-60). In about 1977, they published this research. (DTX HA at 1179; PTX 133 at 902).

The {*30} Wurtmans then applied their theory to humans who complained of craving carbohydrates. (R. Wurtman Tr. pp. 21-22). Those patients were referred to as having "Carbohydrate Craving Obesity" ("CCO"), a term coined by Dr. Judith Wurtman. (R.

Wurtman Tr. p. 22; J. Wurtman Tr p. 161). After directly measuring the food intake of these subjects to determine whether they actually overconsumed carbohydrates, the Wurtmans determined that these patients had a specific appetite for carbohydrates, which occurred at a particular time of day, resulting in an overconsumption of calories and weight gain. (R. Wurtman Tr. pp. 22-24; J. Wurtman 160-61; PTX 132 p. 215-16). Based on this data, the Wurtmans conducted a clinical trial in which they tested whether overconsumption could be suppressed by fenfluramine, which increases brain serotonin release. (R. Wurtman Tr. pp. 22-23; J. Wurtman Tr. pp. 161-62; PTX 132 p. 215-16). In 1983, they first published the results of that clinical study, which showed that fenfluramine suppresses carbohydrate intake. (R. Wurtman Tr. pp. 22-24; J. Wurtman Tr. p. 162; PTX 132 p. 215-16).

Also in the early 1980s, the Wurtmans were issued two patents resulting from their work {*31} on CCO, **U.S. Patent No. 4,309,445** ("the '445 **patent**") entitled "D-Fenfluramine for Modifying Feeding Behavior," and 4,452,815 ("the '815 patent") entitled "Method of Utilizing D,L-Fenfluramine for Modifying Feeding Behavior." (DTX WW (1982), WX (1984)). The '815 patent teaches the Wurtmans' discovery that carbohydrate cravings "tend to occur at characteristic times of the day and are often enhanced by stress or, in women, by premenstrual tension." (DTX WX col. 1, ll. 26-28). The '815 patent also states that patients to be treated with d,l-fenfluramine are characterized by, among other things, "an appetite occurring according to a regular circadian cycle, and the resulting circadian maxima can be in relation to the menstruation cycle." (DTX WW col. 3, ll. 1-3.) Although the Wurtmans suggest in passing that carbohydrate craving could be associated with the menstrual cycle, CCO is not limited to women. In addition, the '815 patent disclosed that the described activity of d,l-fenfluramine "appears to be mediated by the serotoninergic system." (DTX WW at col. 3, ll. 34-35.) Due at least in part to the Wurtmans' research, it was well-known by 1987 that serotonin regulated carbohydrate intake. {*32} (DTX XI (1987)).

In the early 1980s, however, the Wurtmans' theory regarding the relationship between carbohydrate intake and serotonin was not widely accepted by the scientific community. The conventional wisdom was that overweight people overconsumed carbohydrates simply out of habit. (R. Wurtman Tr. pp. 24-25; J. Wurtman Tr. p. 162). To respond to this criticism, the Wurtmans decided to test patient groups whose carbohydrate craving was not habitual. They identified three potential groups: (1) those with Seasonal Affective Disorder ("SAD"), who overconsumed carbohydrates only in the winter months; (2) those who suffered from premenstrual syndrome ("PMS"), n4 who were thought to overconsume sweet or salty carbohydrates during the luteal phase of the menstrual cycle; and (3) those who had nicotine withdrawal after they stopped smoking. (R. Wurtman Tr. pp. 25-26; J. Wurtman Tr. pp. 162-64).

- - -Footnotes- - -4

n4 As used herein, the term "PMS" includes LLPDD/PMDD, in accordance with the Court's claim construction. Additionally, LLPDD and PMDD are used herein interchangeably. (Rapkin Tr. p. 601).

- - -End Footnotes- - -

{*33} To test their theory, the Wurtmans scientifically measured whether SAD subjects overconsumed carbohydrates during the winter months. (R. Wurtman Tr. pp. 26-27; J. Wurtman pp. 164-65). Then, once they demonstrated that this overconsumption pattern did exist, they administered the serotonin-releasing agent fenfluramine to determine whether that agent was effective in treating SAD patients. In 1987, they published the results of their clinical trial, which showed that fenfluramine markedly decreased carbohydrate intake in those patients. (R. Wurtman Tr. p. 27; J. Wurtman Tr. pp. 165-66; DTX XG p. 330). Also in 1987, the Wurtmans were issued **U.S. Patent No. 4,649,161** ("the '161 **patent**") entitled "Method for Treating Depression with D-Fenfluramine." (DTX WZ).

In February 1986, the Wurtmans began to study PMS. (R. Wurtman Tr. p. 28; J. Wurtman Tr. p. 166; PTX 126 (PMS study protocol) p. WURT-000947). Following the same procedure they had established with CCO and SAD patients, the Wurtmans first studied the food intake of women suffering from PMS to determine whether there were differences in the amount and types of food they consumed as compared to women who did not suffer from PMS. There {*34} had been anecdotal reports that women with PMS craved sweet or salty carbohydrates during the luteal phase of the menstrual cycle. (R. Wurtman Tr. pp. 27-28; J. Wurtman Tr. pp. 163-64, 167). However, prior to the Wurtmans' work, no scientific study had measured carbohydrate craving in general in women with PMS. (R. Wurtman Tr. pp. 29-31; J. Wurtman Tr. p. 167; Miller Tr. pp. 499-500).

Next, the Wurtmans prepared a clinical trial protocol proposing: (1) to measure the amount and type of food that women with PMS consumed during the luteal phase and compare it with the amount and type of food

consumed during the follicular phase, and (2) if there was a difference, to determine the effect of the serotoninergic agent fenfluramine on the mood changes and increased carbohydrate consumption of women suffering from PMS. (PTX 126 at WURT-000949). On February 11, 1986, the protocol was submitted to the MIT institutional review board, the committee responsible for authorizing such studies. (R. Wurtman Tr. pp. 28-29; J. Wurtman p. 169; PTX 126 p. WURT-000947). This protocol, however, did not include the serotoninergic agent fluoxetine.

The protocol was approved on April 1, 1986, and the clinical {*35} trial commenced shortly thereafter. (R. Wurtman Tr. p. 32; J. Wurtman Tr. p. 170; PTX 158). Potential patients were examined by a gynecologist and psychiatrist, who used well-established rating scales to confirm a diagnosis of PMS or severe PMS. (R. Wurtman Tr. pp. 32-34; J. Wurtman Tr. pp. 170-71; PTX 126 p. WURT-000955-60). The results of the food intake portion of the study demonstrated that non-PMS women did not alter their caloric intake and did not show a preference for any particular type of food. In contrast, women with PMS had a higher caloric intake and a higher intake of carbohydrates during the luteal phase of their menstrual cycle as compared to control subjects. (R. Wurtman 34:19-35:21, 36:17-37:7; J. Wurtman 167:17-168:21; PTX 89 at WURT-000577). Contrary to what was generally believed prior to their study, PMS patients craved all types of carbohydrates, sweet and salty. (R. Wurtman Tr. pp. 35-36; PTX 89 p. WURT-000577).

Once the intake portion of the study was completed, in the summer of 1986, those patients suffering from PMS participated in the second part of the protocol, the administration of fenfluramine to treat PMS. (R. Wurtman Tr. p.37). At that time, there {*36} were no known effective agents for the treatment of PMS. No one had ever used fenfluramine to treat PMS before, and the Wurtmans did not know what to expect. (R. Wurtman Tr. p. 38; J. Wurtman Tr. p. 171; PTX 1, col. 1, l. 62-col. 2, l. 2). The results from the use of fenfluramine to treat PMS were very positive. (R. Wurtman Tr. pp. 38-40; J. Wurtman 171:23-172:25; PTX 131 at HAM 04592). The patients showed major improvement, not only in carbohydrate cravings, but also in their mood. For the first time "they had something that really made them feel better when they had PMS." (R. Wurtman Tr. p. 38).

In early 1987, having obtained excellent results using fenfluramine, the Wurtmans discussed the possibility of administering another agent that might generate responses similar to those of fenfluramine to some of the PMS subjects who had participated in the fenfluramine study. n5 Dr. Richard Wurtman came up with the idea of fluoxetine, a known serotonin-enhancing agent, having become familiar with the drug from his research and from his work as a consultant to Dr. Ray Fuller at Lilly, the inventor of fluoxetine. (R. Wurtman Tr. pp. 40-41; J. Wurtman Tr. pp. 173-74). At this time, several {*37} clinical researchers had access to fluoxetine and had published clinical trial results on its use in other disorders, which showed that fluoxetine was safe. (R. Wurtman pp. 42-43; 43-44; see DTX AC, GB). Dr. Wurtman testified that he requested a quantity of fluoxetine directly from Dr. Fuller, his friend of twenty years, as he had done previously approximately ten or fifteen times over the years. (Id. p. 94)

---Footnotes---5

n5 Teva challenges Dr. Richard Wurtman's memory on this point at his deposition, but we find his trial testimony, which was corroborated by Dr. Judith Wurtman, credible. (J. Wurtman Tr. p. 174). The Wurtmans' testimony required them to remember various events that happened approximately fifteen to seventeen years ago, events which resemble in large part other clinical trials in which they have participated over the years. Such a time lapse would allow for some slippage in their memories as they piece back together again the events at issue in this trial.

---End Footnotes---

Dr. Richard Wurtman did not, however, have {*38} enough fluoxetine for a full-blown clinical trial. Therefore, in about May 1987, he conducted a case study of the treatment of PMS using fluoxetine. (R. Wurtman Tr. p. 41). At trial, Dr. Wurtman testified that the fluoxetine came directly from Dr. Fuller and that he never asked Dr. Fuller for large amounts of the drug; Dr. Wurtman's deposition revealed that at the time of the case study, Dr. Wurtman's graduate student was also doing research with fluoxetine, but it was expressly limited to use on animals. (Id. p. 92-93). Because Dr. Wurtman and his graduate student had made a formal request of Lilly for the fluoxetine used in the rat study, had complied with all of the conditions placed on that request, and through that compliance did not indicate that the fluoxetine was used to treat humans, we conclude that the fluoxetine likely came from Dr. Fuller to Dr. Wurtman, as one insider to the other. (See R. Wurtman Tr. pp. 90-94.)

Although Dr. Wurtman testified that he conceived of a protocol for his case study, which he showed to four n6

of his patients to inform them of the experimental value of the case study, he never filed a protocol with the institutional review board at {*39} MIT, and if such a protocol ever existed, it no longer exists. The patients did not sign informed consent forms. (R. Wurtman Tr. pp. 43, 78, 89; J. Wurtman Tr. p. 174). It is Dr. Wurtman's belief that a disclosure to MIT was not necessary because MIT was not involved in this case study and it took place off-campus, at his apartment/office. (R. Wurtman Tr. pp. 44, 77-78, 85). n7

---Footnotes---6

n6 At his deposition, Dr. Richard Wurtman testified that he gave fluoxetine to two women, not four. However, after reconstructing the different ways in which he tested the drug, Dr. Wurtman realized that his tests would have required four subjects, not two. (R. Wurtman Tr. pp. 82-84).

7

n7 With regard to Dr. Richard Wurtman's testimony that his case study was a "compassionate use," (R. Wurtman Tr. pp. 77-79, 106), we credit his understanding of the case study, but note that it likely would not have been the FDA's view of that use. Under a "compassionate use" exemption, a physician may apply to use a research drug, one not approved by the FDA, to treat a life-threatening condition where no alternative drug is available. (See 52 F.R. 19466 (1987); Miller Tr. pp. 248-49.) In May of 1987, the use of a non-FDA approved drug was only allowed to be under clinical investigation for "serious or immediately life-threatening disease condition" where no alternative drug or other therapy is available and where the drug is under investigation in a controlled clinical trial with an investigational new drug application filed with the FDA. (See 52 F.R. 19466 (1987).)

The parties did not argue what effect, if any, any alleged illegality as to Dr. Wurtman's actions would have on the validity of the '998 patent. The patent examiner was as aware of Dr. Wurtman's work as we are. Throughout the trial and in its briefs, Teva stresses the unlikelihood of Dr. Richard Wurtman's story of invention. However, while we noted that Dr. Wurtman's demeanor at trial was rather arrogant, as if the law had gotten in the way of the development of his research and the treatment of his patients, we did not find him to be untrustworthy. See also, supra, note 22.

---End Footnotes---

{*40} Dr. Richard Wurtman administered fluoxetine to one patient on a continuous basis every day of the month, during three menstrual cycles, and to the other three patients as reported in Example II of the '998 patent. (PTX 1; R. Wurtman Tr. pp. 44-45). To evaluate the effect of fluoxetine to treat PMS, the patients in the case study utilized the same PMS questionnaire that was used in the fenfluramine protocol. (Id. p. 44). Dr. Wurtman did not retain copies of those questionnaires. (Id. p. 90). Dr. Wurtman testified that the patients in the fluoxetine case study were "euphoric" over the beneficial effects of the fluoxetine and received the same improvement and relief from their PMS symptoms as was obtained using fenfluramine. (Id. p. 45). Dr. Judith Wurtman did not participate in the fluoxetine case study (she is not a physician), and learned of the results only upon the filing of the '998 patent. (J. Wurtman Tr. pp. 174-75, 180-81.) In fact, no corroboration exists for Dr. Richard Wurtman's case study with one important exception, that is, the '998 patent.

After he analyzed the results of the fluoxetine case study, Dr. Richard Wurtman ultimately disclosed them to MIT, along {*41} with the results of the fenfluramine clinical trial, because he regarded them as an outgrowth of the fenfluramine clinical trial. (R. Wurtman Tr. p. 47). Together with the data from the fenfluramine clinical trial, the fluoxetine case study results formed the basis of the '998 patent application. (R. Wurtman Tr. pp. 45-47). As shown in the '998 patent, on average, women who took fenfluramine had more than a 50 percent reduction of symptoms based on their Hamilton Depression Scale ("HAMD") scores, and almost 100 percent reduction in their PMS Symptom Rating Scale scores. ('998 patent (PTX 1), col. 6, Tables 1-2). Likewise, patients who were treated with fluoxetine experienced a 75 percent improvement in mood ratings and a 70 percent improvement in appetite ratings, which results have been confirmed by other researchers. (R. Wurtman Tr. pp. 46-47; '998 patent (PTX 1), col. 6, ll. 50-59. See, e.g., PTX 60 pp. 1531-32; PTX 134 at Fig. 1, Fig. 2; PTX 40, Tables 1-4).

MIT authorized the filing of a patent application covering the Wurtmans' work. (R. Wurtman Tr. pp. 45, 47). On October 22, 1987, MIT filed U.S. Patent

Application Ser. No. 111,771, naming Richard J. Wurtman and Judith {*42} J. Wurtman (collectively, "the Wurtmans") as inventors. On September 15, 1988, MIT filed U.S. Patent Application Ser. No. 244,944 as a continuation-in-part of Ser. No. 111,771. Although the patent at issue in this case, **U.S. Patent No. 4,971,998** ("the **'998 patent**"), issued from Ser. No. 244,944, the effective filing date of the **'998 patent** is October 22, 1987. During prosecution of the **'998 patent**, the patent examiner reviewed, among other things, patents and publications disclosing the use of fluoxetine to treat depressive and anxiety disorders and the use of fenfluramine to treat SAD and CCO, and publications discussing blood serotonin levels in PMS patients. The **'998 patent**, entitled "Methods For Treating the Premenstrual or Late Luteal Phase Syndrome," issued on November 20, 1990, to MIT as the assignee of the Wurtmans.

V. The State of the Art in 1987

A. The Nature of PMS

The **'998 patent** is directed to the use of fenfluramine and fluoxetine to treat PMS. Claim 2, the only claim at issue, states:

A method for treating disturbances of mood, disturbances of appetite, or both, associated with pre-menstrual syndrome, comprising administering to a woman prior {*43} to the onset of her menstrual period, a composition consisting essentially of approximately 5 mg to approximately 120 mg of fluoxetine.

(**'998 patent** (PTX 1), col. 7, ll. 7-12.).

The Court has construed the claim terms "pre-menstrual syndrome," "disturbances of mood," "disturbances of appetite," and "prior to the onset of her menstrual period" as follows:1) the term "pre-menstrual syndrome" as used in Claim 2 of the **'998 patent** includes LLPDD/PMDD; 2) the term "disturbances of mood" we construe to mean negative changes in a person's normal mood associated with PMS; 3) the term "disturbances of appetite" we construe to mean negative changes to a person's normal appetite associated with PMS; and 4) "prior to the onset of her menstrual period" we construe to include not only late-luteal phase dosing regimens, but also all dosing regimens that begin prior to the onset of a woman's menstrual period, including those that go on continuously thereafter.

(PTX 192 at 10, Dk # 119). n8 "PMDD" and "LLPDD" are terms that can be used interchangeably and refer to a severe type of PMS. (Rapkin Tr. pp. 601-02; Brown Tr. pp. 731-32).

- - -Footnotes- - -8

n8 A guide to the phases of a woman's menstrual cycle:

Women of child-bearing age experience monthly menstrual cycles, which prepare the body for a potential pregnancy. A woman's menstrual cycle begins on the first day of her period. Towards the beginning of the cycle, a hormone called follicle stimulating hormone ("FSH") is released from the brain. FSH stimulates the growth of 15 to 20 of the hundreds of thousands of immature eggs contained in a woman's ovaries. Each of the growing eggs is surrounded by a sac known as a follicle. As the follicles mature, they begin producing a hormone called estrogen, which stimulates the lining of the uterus, or endometrium, to thicken. One of the growing eggs will mature more quickly than the others and suppress the growth of the other eggs. (Miller Tr. pp. 210-11.)

At about midpoint in the cycle, a hormone called luteinizing hormone causes the dominant follicle to release its egg in a process called ovulation. After the egg is released, it enters the fallopian tube and journeys toward the uterus. If the egg is not fertilized, the endometrium begins to break down. The dead endometrial cells, along with blood and mucus, are discharged as menstrual flow. (Miller Tr. pp. 211-13.)

The menstrual cycle takes an average of 28 days. The follicular phase of the cycle begins with menstruation and ends with ovulation. Assuming a 28-day cycle, the follicular phase stretches from approximately day 1 to day 14. The luteal phase of the cycle begins with ovulation and ends with menstruation. Again, assuming a 28-day cycle, the luteal phase stretches from approximately day 14 to day 28 of the cycle. (Miller Tr. pp. 213-14.)

- - -End Footnotes- - -

{*44} Under the Court's definition, PMS includes PMDD and is a condition that begins during the luteal phase and remits during the follicular phase. (Endicott Tr. p. 1055; see also Smirz Tr. p. 1299). Teva's expert, Dr. Rapkin, confirmed at trial what she had written in 1987, that PMS was defined as "a cyclical disorder manifested by diverse physical and psychological

symptoms in the luteal phase with relief soon after the onset of menses" and characterized by "a symptom-free week." (Rapkin Tr. pp. 588-90; DTX FF). Indeed, the "on-and-off nature" of PMS is an essential requirement of the disorder. (Endicott Tr. p. 1055; Smirz Tr. p. 1299). Therefore, a disorder related to PMS, premenstrual exacerbation, in which an underlying condition worsens during the luteal phase, would not, however, fall within the definition of PMS because there are no symptom-free days. (Endicott 1067:2-24, 1109:5-16; Smirz Tr. pp. 1303, 1305; Rapkin Tr. pp. 599-600, 601; see also Entry on Claim Construction pp. 6-7, 12 endeavoring not to broaden the claim term PMS beyond its plain meaning in 1987).

The Court construed the term PMS to be an "umbrella" term in that PMS can cover a number of different symptoms {*45} or complaints, and does not require that any specific symptom or complaint be present. (Endicott Tr. p. 1055; Smirz Tr. p. 1302). As construed by the Court, the term PMS encompasses over 150 different symptoms that are known to track in some women during the premenstrual phase. (Miller Tr. p. 215; Smirz Tr. p. 1302.) These symptoms can include both mood symptoms (e.g., depression, anxiety, or irritability) and physical symptoms (e.g., bloating, weight gain, and food cravings). (Smirz Tr. pp. 1302-03; Miller Tr. pp. 216-17; 226-27; R. Wurtman Tr. pp. 35-36, 56). Further complicating a diagnosis of PMS is the fact that any one of its symptoms may occur in many different diagnostic contexts. (See Miller Tr. p. 254). The treatment of that symptom depends on the diagnostic context in which it occurs. (Endicott Tr. p. 1058; Smirz pp. 1303-04). PMS is not a subset of depression. (Rapkin Tr. pp. 607-608). What may be a symptom of PMS, e.g., depression or depressed mood, may also exist as a stand alone disease, e.g., major depression, which would require different treatment. (R. Wurtman Tr. p. 129-30.)

B. The Cause of PMS

As of October 1987, the etiology of PMS was unknown. (Miller {*46} Tr. pp. 455-56; Rapkin Tr. p. 623; Endicott Tr. pp. 1072-73). In 1985, David S. Janowky and Jeffrey Rausch published *Editorial: Biochemical hypotheses of premenstrual tension syndrome,"* 15 Psych. Med. 3-6 (1985) ("Janowsky"), in which they canvassed the knowledge landscape of PMS. Janowsky stated that researchers have tried to correlate changes in the menstrual cycle with changes in hormones (e.g., estrogen, progesterone, prolactin, mineralocorticoids and adrenocortical hormones), electrolytes, neurotransmitters (e.g., opioid polypeptides, cholinergic mechanisms, catecholamine alterations, and serotonin) and somatic parameters. (DTX CQ pp. 3-6; see also Endicott Tr. p. 1077; Smirz Tr. p. 1308.) Although Janowsky suggests that the same neurotransmitter thought to regulate affective disorders might modulate PMS, he admits that evidence of this connection is "by no means conclusive." (Id. p. 5). In November 1985, William R. Keye, Jr., stated, "Unfortunately, a survey of the medical and behavioral literature on premenstrual syndrome only points out the confusion surrounding this disorder." *Medical Treatment of Premenstrual Syndrome*, 30 Can. J. Psychiatry 483-87 (1985); {*47} (DTX CU p. 483). Even the **'998 patent** recognizes that as of its filing date there were multiple theories as to what caused PMS, and that none of those theories had been substantiated. (PTX 1, col. 1, ll. 37-61; R. Wurtman Tr. pp. 49-50). n9

---Footnotes---9

n9 Janowsky and Keye were not before the patent examiner, but as just described, they teach nothing that conflicts with the '998 patent.

---End Footnotes---

A leading theory in 1987 was one related to sex hormone changes (*i.e.*, progesterone) linked to a woman's menstrual period. (Endicott Tr. pp. 1077, 1153-54; Smirz Tr. p. 1307-08). Another, relatively new theory, was serotonin deficiency. Looking specifically at the hypothesis that a serotonin deficiency causes PMS, we determine what was known about that theory as of 1987. Serotonin was first suggested as a possible cause of PMS in 1979. (See, e.g., DTX GX). Reduced serotonin function was also known as of 1987 to result in symptoms of anxiety and depression. (See DTX A, WY). In addition, the Wurtmans own research demonstrated that {*48} serotonin regulated carbohydrate intake. (DTX WX).

As of October 1987, those skilled in the art were just beginning to discover the relationship between affective disorders and PMS. In 1985, Janowsky wrote that "[a] logical strategy for studying (premenstrual tension syndrome ("PMT")) may be to assume that the same neurotransmitter and neuromodulators thought to regulate affective disorders are those which also modulate PMT." (DTX CQ p. 5; see also DTX GX (March 1979) p. 361 ("Lowered levels of serotonin . have consistently been associated with depressive states. Thus, one would predict depression just prior to menstruation, with some effect continuing for about a week.")). Also, in a November 1985 article, Renate DeJong, *et. al.*, stated that "the results of several

studies suggest that a special relationship exists between premenstrual syndromes and major psychiatric disorders, particularly affective illness." *Premenstrual Mood Disorder and Psychiatric Illness*, 142 Am. J. Psychiatry 1359 (1985). (DTX BC p. 1359). n10

---Footnotes---10

n10 In a study published in June 1987, Parry was motivated to test the effect of sleep deprivation, a known therapy for major depressive disorder, on PMS because "premenstrual syndrome and affective disorders may be related illnesses." (DTX DV p. 808). Although the Parry reference was not published more than a year before the effective date of the '998 patent and cannot be considered in our obviousness analysis, it is relevant in deciding the level of ordinary skill in the art.

---End Footnotes---

{*49} While PMS and affective disorders such as anxiety and depression share some common symptoms, they also have significant differences. For example, PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. (Rapkin Tr. pp. 588, 591-92; Blier Tr. pp. 1393-94, 1395). In 1987, it had not been proven that people suffering from PMS had the same biological characteristics as people suffering from depression. For example, PMS affects only women. (Rapkin Tr. pp. 604-05). PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may experience early morning awakenings and evidence a lack interest in the world around them, and not all PMS patients are depressed). (Brown Tr. pp. 745-49). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

Also in the early 1980s, clinical researchers attempted {*50} to measure the serotonin functioning in women with PMS to determine if a serotonin deficiency caused PMS. In a 1984 article, *Serotonin Levels and Platelet Uptake during Premenstrual Tension*, 12 Neuropyschobiology 16-18 (1984), Dorothy L. Taylor, *et al.*, studied the correlation between the severity of a woman's PMS and the decrease in that woman's peripheral serotonin levels. (DTX GP p. 16). She compared a woman's premenstrual platelet serotonin levels with her postmenstrual platelet serotonin levels, and the degree of change was correlated with the degrees of distress experienced by the patient pre-and post-menstrually. Building on Taylor's findings, in a study published in October 1987, n11 Andrea J. Rapkin, *et al.*, compared women with PMS to asymptomatic women and found changes in serotonergic function in patients with PMS. *Whole-Blood Serotonin in Premenstrual Syndrome*, 70 Obstetrics & Gynecology 533 (1987). (DTX FF pp. 536-37). Contrary to what is usually attributed to her, Rapkin did not find that PMS patients' serotonin levels decreased premenstrually. Rather, Rapkin showed that women with PMS had lower serotonin levels throughout the menstrual cycle, as compared {*51} with women who did not have PMS. (Blier Tr. pp. 1367-69; DTX FF at Fig. 1).

---Footnotes---11

n11 Although Rapkin's article does not qualify as **102(b)** prior art because it was not published more than one year before the filing of the **'998 patent**, this article was before the patent examiner.

---End Footnotes---

Dr. Blier, a serotonin expert testifying for Lilly, discounts Taylor's work because of "a major methodological flaw." Taylor only measured serotonin changes in women with PMS, and made no comparison of PMS patients with a control group of women who did not have PMS. (Blier Tr. pp. 1365-66; Endicott Tr. p. 1097). In addition, Dr. Blier challenges Rapkin's findings by showing that she did not control for diet, which was known in 1987 to affect serotonin. (Blier Tr. pp. 1369-70). Dr. Blier also argues that although blood platelets model serotonin neurons in the brain, changes in serotonin levels in the blood do not indicate the same type of activity in the brain, a fact Rapkin also noted in her article. (Blier Tr. pp. 1360-63; DTX FF p. 537; {*52} see also R. Wurtman Tr. pp. 59-61).

Although we credit Dr. Blier's testimony as to the mechanics of serotonin functioning and note his criticisms of the Taylor and Rapkin articles, we conclude that there is substantial evidence that those of ordinary skill in the art relied, at least in part, on Taylor and/or Rapkin, including the authors of the DSM-IV. (Miller Tr. pp. 319-20; see, e.g., DTX GG p. 242; WR p. 616;QQ p. SA 1520 1707; Endicott Tr. pp.

1189-94). These references, however, suggest only the involvement of serotonin with PMS, nothing more. (See Brown Tr. pp. 736-37; Endicott Tr. p. 1189). Neither doctor conducted a clinical trial of any drug, including fluoxetine. Furthermore, Rapkin specifically states that as of 1987 further studies were necessary "to elucidate the association between diminished peripheral serotonin and premenstrual syndrome."

C. The Treatment of PMS

Because the state of the art in 1987 was so uncertain and confused, doctors, n12 in an effort to treat patients presenting with PMS for the disorder as a whole, would nonetheless most likely have to target predominant or groups of symptoms for treatment. (See Endicott Tr. pp. 1155-56, 1158-59; {*53} Smirz Tr. pp. 1317-20, 28; Miller Tr. pp. 267-70). As of 1987, the only treatment that was believed to alleviate PMS as a syndrome would be directed at preventing ovulation, but that was not considered an acceptable treatment. (Endicott Tr. p. 1081; Miller Tr. p. 467; Smirz Tr. p. 1308). In a 1982 article entitled *The Premenstrual Syndrome: A Review of the Present Status of Therapy*, 24 Drugs 140-49 (1982), P.M.S. O'Brien (not an assumed name as we were informed) discusses the need for individualized assessments because of the wide variety of symptoms with which patients present. He then suggests that physicians treat their patients first with oral contraceptives or progestagen, and then, if neither of those options is effective, physicians should "determine the most distressing symptom or symptom type." (DTX DP pp. 147-48).

---Footnotes---12

n12 We find that these doctors, obstetricians, gynecologists, family physicians and psychiatrists, who regularly treat patients suffering from PMS qualify as those of ordinary skill in the art. They would be looking to solve a problem, so they would make themselves familiar with the relevant literature (Miller Tr. pp. 279-80), but they would be community-based (Endicott Tr. p. 1054). Physicians who conduct only clinical research on PMS, however, would be considered persons of more than ordinary, or extraordinary, skill in the art. (Brown Tr. pp. 761; Endicott Tr. p. 1054).

---End Footnotes---

{*54} As of 1987, a wide variety of drug therapies had been proposed for different groups of symptoms. If depression was the predominant symptom, the experts counseled caution. O'Brien found that, in general, "psychoactive drugs do not play an important role in treating the premenstrual syndrome." (DTX DP pp. 142, 148). As of the time of Keye's November 1985 article, "adequate trials of [MAO] inhibitors [and] of tricyclic antidepressant in premenstrual syndrome have not yet been reported. . While psychoactive drugs may relieve a selected premenstrual symptom such as depression or anxiety, none would appear to be broad enough in its effect to provide satisfactory relief for women with severe and multiple symptoms." (DTX CU pp. 483-84). Furthermore, the relief available from the antidepressants available at the time, tricyclic antidepressants and MAO Inhbitiors, had to be weighed against their unpleasant side effects. (Miller Tr. pp. 267-68). For example, such risks and side effects include a risk of suicide with tricyclics (PTX 10 at 2627) and drug interactions with MAOIs (PTX 10 at 2563). ACOG did not recommend treatment of PMS with antidepressants until 1995. (Smirz Tr. pp. 1332.) {*55} Also, physicians were hesitant to prescribe antidepressants for treatment of PMS patients because of the perceived stigma associated with taking them. (Tollefson Tr. pp. 905-07; Smirz Tr. p. 1302).

Another treatment which was known to relieve, at least in part, the mood symptoms of PMS, but not the physical symptoms, was alprazolam, which is an anti-anxiety agent. However, alprazolam creates harmful side effects such as palpitations, tremors and seizures. (Miller Tr. pp. 465-66; Endicott Tr. pp. 1082-83). Additionally, physicians were not particularly comfortable using alprazolam to treat PMS in part because it is addictive. (Endicott Tr. pp. 1082-83).

Proponents of the serotonin hypothesis recommended testing agents that influence the serotoninergic pathway, namely tryptophan (DTX CQ p. 6; DTX FF p. 537) or chlorimipramine. (DTX CQ p. 6), or trazodone hydrochloride (DTX FF p. 537). Chlomipramine had been on the market since 1982. (Miller Tr. p. 461). As of October 1987, tryptophan had been shown to be an ineffective agent for treating PMS. In 1984, Dr. Endicott conducted a clinical trial using tryptophan and concluded it was totally ineffective in treating PMS. (Endicott Tr. pp. {*56} 1100-01; PTX 21 at 120). No one, however, had suggested the use of fluoxetine or fenfluramine, two known serotonin-enhancing agents. (Miller Tr. p. 404; Blier Tr. p. 1381-82; see also DTX WW (the '815 patent) at col. 3, ll. 34-35 (the described action of d,l-fenfluramine "appears to be mediated by the serotonergic system")).

With regard to fenfluramine, a non-psychotropic drug, Dr. Miller testified that it would be "highly unusual for

a psychiatrist to use fenfluramine for any purpose." (Miller Tr. pp. 501-02). In addition, she is unaware of any OB/GYN who used fenfluramine to treat PMS prior to the Wurtmans. (Id. pp. 503-04.) In addition, Dr. Blier testified that the prior art teaches away from the use of fluoxetine to treat PMS. According to Rapkin's 1987 data, serotonin levels in whole blood were lower for women with PMS as compared to control subjects. Thus, one skilled in the art would want to increase whole blood serotonin levels. Fluoxetine, however, does the opposite; it decreases, not increases, whole blood serotonin. (Blier Tr. pp. 1381-82; PTX 52 at 14). Therefore, one skilled in the art who was relying on Rapkin's data would not have been motivated to use fluoxetine {*57} to treat PMS. (Blier Tr. pp. 1380-81, 1423-24).

As of October 1987, what was known about fluoxetine was that it was an effective treatment of depression and anxiety. Fluoxetine had been used in clinical trials since 1976, and studies confirming its efficacy in the treatment of major depressive disorder were published in 1985. (DTX AV, GB; Miller Tr. pp. 405-06). None of these prior art references, however, suggested the use of fluoxetine to treat PMS. Given the treatment options described above, fluoxetine, with its high level of effectiveness and improved side effect profile, was a "therapeutic triumph." (Brown Tr. p. 774).

Although the Wurtmans were the first to propose fluoxetine as a PMS therapy in October 1987, Teva asserts that several other people arrived at the same conclusion at about the same time. On February 5, 1988, Wilma Harrison, et. al. ("the Harrison group"), proposed the *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study.* (DTX OW). About five months later, on July 12, 1988, Andrea B. Stone and Dr. Brown, Teva's expert in this case ("the Stone group"), proposed an *Assessment of Fluoxetine in the Treatment of Premenstrual* {*58} *Syndrome.* (DTX NX; published as *Fluoxetine in the Treatment of Premenstrual Syndrome,* 26 Psychopharmacol. Bull. 331-35 (1990), DTX GJ). n13 As both of these studies were proposed after January 1, 1988, however, they likely reflect the subtle shift in the state of the art that occurred on that date when the FDA approved fluoxetine (Prozac) for the treatment of depression.

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n13 In July 1990, Karl Rickels, et al., published *Fluoxetine in the Treatment of Premenstrual Syndrome,* 48 Current Therapeutic Res. 161-66 (1990) ("Rickels"). (DTX FN.) As Rickels did not express interest in using fluoxetine to treat patients suffering from PMS until June 30, 1989, almost two years after the filing of the **'998 patent**, and did not publish his findings until July 13, 1990, we conclude that his contribution is too far removed to be considered probative of simultaneous invention. (See also D-Dem-H, listing physicians proposing the use of fluoxetine after 1989). By mid-1989, the Wurtmans and the Stone group were already speaking publically about and publishing their findings. (See J. Wurtman 185-87; DTX HM, XQ).

Teva also offers four letters to the editor offering anecdotal evidence of the use of fluoxetine to treat PMS prior to the issuance of the **'998 patent.** However, as stated at trial, these exhibits, DTX BQ, CO, DE and DY, are hearsay "plain and simple," and thus, not be considered evidence of simultaneous invention. See Tr. pp. 1181-82.

---End Footnotes---

{*59} Teva asserts that before FDA approval of fluoxetine, Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS. Teva, however, does not support this allegation with evidence. In all of the voluminous exhibits that the parties have provided us, we see no letter dated before the filing of the **'998 patent** from a clinician to Lilly asking Lilly for fluoxetine with which to study the treatment of PMS or any letter from Lilly to any clinician denying him or her the same. In fact, when Drs. Stone and Brown proposed their study to Lilly in 1988, Lilly agreed to fund it even though Lilly indicated that it would not be seeking an indication for fluoxetine in the treatment of PMS. (See DTX XN, XO, XP, YB). n14

---Footnotes---14

n14 In 1992, after Lilly become aware of the **'998 patent**, when Drs. Brown and Stone applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. (DTX OC, OD, OE).

---End Footnotes---

{*60} Although the subjects in the Harrison protocol had premenstrual exacerbation not PMS, the two study proposals offer, generally speaking, the same motivation to use fluoxetine to treat PMS: (1) patients with premenstrual depression have symptoms associated with affective disorders; (2) "pathophysiologic links between PMS and mood disorder" suggested that an agent like fluoxetine, which would lead to increased serotonergic activity may provide symptomatic relief from [PMS];" (3) fluoxetine had advantages over the then-existing antidepressants because it could address the increased appetite and sleep often found in patients with PMS; and (4) fluoxetine had a "relatively low incidence of troubling side effects" which would be "particularly suitable in treatment of women who are asymptomatic 75% of the time." (DTX XK; Brown Tr. pp. 666-71; see also DTX OX p. 2).

The scientific evidence that Dr. Harrison and Dr. Stone each relied on in deciding to use fluoxetine to treat PMS would have been available as of October 1987. (Brown Tr. pp. 680, 733-36.) However, the Harrison group and the Stone group would have viewed it differently from one of ordinary skill in the art. Each group, at {*61} the time it conducted is fluoxetine study, seriously considered other agents. After a review of the relevant literature, Dr. Stone's group decided against progesterone (Brown Tr. pp. 663-64), and the Harrison group was also conducting another study using nortriptyline to treat premenstrual depression (DTX FN p. 166). However, we conclude that the Harrison group and the Stone group would have been more likely to choose fluoxetine than another agent because one member of each group, Dr. Quitkin in the Harrison group and Dr. Brown in the Stone group, had participated in Lilly's clinical trials of fluoxetine to treat major depressive disorder, and thus would have been more familiar with the drug than would be one of ordinary skill in the art.

Dr. Brown testified that he had "more than a reasonable expectation" of success in using fluoxetine to treat PMS. (Brown Tr. pp. 820-21.) He explained, "That is why we did the study. Otherwise we wouldn't have done it." (Id. p. 821). Perhaps Dr. Brown's confidence was due to his superior knowledge of the efficacy of fluoxetine. Other clinical researchers, however, know that not all research will return the hoped for result (Endicott Tr. pp. 1101-02 describing {*62} the disappointing results of her tryptophan study), and do not profess such optimism in the results of their work at its outset. (R. Wurtman Tr. p. 38; J. Wurtman Tr. p. 171).

VI. Sarafem(R)

MIT, the original owner of the '**998 patent**, exclusively licensed the '**998 patent** to Interneuron on February 13, 1996. On June 19, 1997, Interneuron exclusively sub-licensed the '**998 patent** to Lilly. Armed with sufficient information about the safety and efficacy of fluoxetine in the treatment of PMS, Lilly finally decided to pursue commercial opportunities in that market. (See Tollefson Tr. p. 904.) Lilly offers this second license, which allegedly demonstrates the commercial value that it places on Sarafem, as objective evidence of the nonobviousness of the '**998 patent**.

Teva responds citing the testimony of its licensing expert, Mr. Gould. Mr. Gould testified that the 1997 license is not evidence of nonobviousness for two reasons, one of which we adopt. First, Mr. Gould opined that Lilly did not expect actually to have to pay running royalty rates in the amounts stated in the license (5% and 20%), an opinion with which Lilly's expert, Mr. Tate, disagrees. We need not determine {*63} the effective royalty rate for the '**998 patent**, however, because we agree with Mr. Gould's second point that the '**998 patent** would have had considerable value to Lilly regardless of its validity. n15

- - -Footnotes- - -15

n15 We do not intend to suggest that Lilly at any time thought the patent was invalid. Rather, we conclude only that the 1997 license is not objective evidence of nonobviousness. Substantial evidence exists that Lilly respected the validity of the '**998 patent** before licensing it, and that Lilly licensed it because Lilly believed it would be a commercial success. For example, in 1992, when Drs. Brown and Stone applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. (DTX OC, OD, OE).

- - -End Footnotes- - -

Mr. Gould testified that, generally, there are two reasons a company may take a license: (1) for defensive purposes to prevent it from being sued as an infringer by the patentee; or (2) for offensive purposes {*64} to prevent others from entering the marketplace. (Gould Tr. pp. 1018-19.) Lilly could use the license offensively whether or not it believed the license to be valid. Once Lilly licensed the '**998 patent**, Lilly could list it in the Orange Book with

respect to Sarafem. Lilly then would have standing to bring suit for infringement against a generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months. The estimated sales value to Lilly of being the exclusive marketer of Sarafem was about $ 580,000,000. (Gould Tr. pp. 1018-23). Thus, we conclude that while the 1997 license had considerable value to Lilly, it is not evidence of nonobviousness.

Having licensed the '998 patent, on December 21, 1998, Lilly filed a Supplemental New Drug Application ("sNDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and market the use of fluoxetine to treat Premenstrual Dysphoric Disorder ("PMDD"). On July 6, 2000, Lilly received approval from the FDA to manufacture and market fluoxetine under the tradename Sarafem for treatment of Premenstrual Dysphoric Disorder ("PMDD"), a severe form of Premenstrual Syndrome ("PMS"). In August 2000, {*65} Lilly began marketing fluoxetine under the tradename Sarafem. (Dkt. 167).

From August 2000 through December 2002, sales of Sarafem in the United States totaled more than $ 176 million (Tate Tr. pp. 1216, 1222-23; PTX 156), and Sarafem was the market share leader for the treatment of PMDD. (Smith Tr. p. 951; PTX 120 at SA 1508 806). n16 However, Dr. Schmittlein, Teva's marketing expert, testified that Sarafem was not a commercially successful product "by Lilly's standards" because sales figures did not meet expectations. (Schmittlein Tr. pp. 1251-52, 1257; DTX RP p. SA 5 35). Dr. Schmittlein determined "Lilly's standards" from a speech made in 2002 by Jonathan Northrup, the Director of Strategic Asset Management for Lilly, in which he said that one of his primary responsibilities "over the past three years is really trying to exit the market from the $ 300 million type of product." (DTX SO at 24.)

- - -Footnotes- - -16

n16 The parties use data from August 2000 to December 2002, presumably the most recent figures available. Neither party introduced any evidence tending to show that this data is no longer representative of the market for Sarafem(R).

- - -End Footnotes- - -

{*66} Lilly is an international pharmaceutical company; its business strategies are not representative of what the broader pharmaceutical market would deem a commercial success. In fact, we find persuasive the patent certification letter that Teva sent to Lilly on February 19, 2002, which declared Sarafem to be a "commercially successful product" due in large part to the fact that "physicians felt comfortable prescribing Sarafem for PMS because of their familiarity with prescribing Prozac for depression." (PTX 98 at p. 9 or p. TEV-SA 06815; Schmittlein Tr. pp. 1285-86). Dr. Schmittlein also attempted to compare the sales of Sarafem to those of Prozac and Lipitor(R). (Schmittlein Tr. pp. 1254-57). Lipitor, the top-selling drug for 2002, lowers cholesterol; as Lipitor has nothing to do with PMS, we find its sales figures unhelpful. Dr. Schmittlein testified that Sarafem did not perform as well in its market (PMDD) as Prozac performed in its market (depression). However, because Prozac did extraordinarily well in its market, we don't find that to be a fair standard by which to evaluate Sarafem either.

Sarafem's prescription data supports a finding of commercial success. (PTX 120). Total prescriptions {*67} of Sarafem remained fairly constant, with only a slight decline, from 2001 to 2002. Repeat prescriptions of Sarafem, which Lilly's marketing expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 compared to 2001 and remained stable through 2002, even though a competitor, Zoloft(R), was approved to treat PMDD in May 2002. (Smith Tr. p. 955-56; PTX 182 at SA 3542-44; PTX 120 at SA 1508 804). New prescriptions, which Dr. Schmittlein opined are the most important indicators of future product success, remained relatively stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). (Schmittlein Tr. pp. 1265-66). After the introduction of Zoloft to the market, the number of new Sarafem prescriptions declined slightly for the rest of 2002; however, Sarafem remained the market leader. (PTX 120 p. SA 1508 806).

Dr. Schmittlein opined that whatever success Sarafem did enjoy was attributable to Lilly's marketing efforts, and that in the absence of any marketing and advertising, the sales of Sarafem would drop to near zero by 2005. (DTX {*68} RV at SA 1508 809; Smith Tr. pp. 989-90; Schmittlein Tr. pp. 1267-69). Dr. Schmittlein offers many figures to describe how much money Lilly spent marketing Sarafem. (Schmittlein Tr. pp. 1259-63). For example, he asserts that approximately 80 percent of the $ 75.4 million Lilly spent developing Sarafem consisted of marketing expenditures. Again, however, Dr. Schmittlein does not identify a drug comparable to Sarafem so that we may understand these numbers in context. Considering that much of Sarafem's product development would have been coincident with the development of Prozac, spending 80 percent of development costs on

marketing may not have been out of line. We also question the basis for the near zero sales figure (*i.e.*, what were the author's assumptions) and what would happen to the sales of a comparable drug in the absence of advertising.

In any case, as stated above, prescriptions of Sarafem remained relatively stable from 2001 to 2002, even though Lilly ended its direct-to-consumer marketing campaign in April 2001 and decreased its sales force from 1700 representatives in 2001 to 1020 in 2002. (DTX RV at SA 1508 818; Schmittlein Tr. p. 1261). Accordingly, we are convinced {*69} that Sarafem's commercial success derived from the merits of the drug rather than the marketing activities by Lilly.

VII. History of This Lawsuit

Lilly's sNDA for Sarafem contained a certification that the '998 patent covers the method of use of fluoxetine for which approval was being sought. Based on Lilly's certification, the FDA listed the '998 patent in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluation," commonly referred to as the "Orange Book," as covering Sarafem. On November 30, 2001, pursuant to 21 U.S.C. § 355(j), Teva filed an Abbreviated New Drug Application ("ANDA") seeking approval to engage in the commercial manufacture, use and sale of a generic version of Sarafem for the treatment of PMDD prior to the expiration of the '998 patent. Teva's ANDA included what is referred to as a "Paragraph IV" certification, which pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) stated that the '998 patent is "invalid, unenforceable, or not infringed by the manufacture, use or sale of Teva's fluoxetine [product]."

On April 5, 2002, Lilly sued Teva for infringement of the '998 patent. On June 17, 2003, Teva {*70} withdrew its patent misuse counterclaim. (Dk # 115). In view of our July 21, 2003 Entry on Claim Construction, on August 8, 2003, Teva stipulated to infringement of Claim 2 of the '998 patent under 35 U.S.C. § 271(b) for purposes of trial. This stipulation was subject to Teva's right to appeal the Court's claim construction decision, the stipulation of infringement, and any consequent finding of infringement. On May 12, 2003, Magistrate Judge Shields issued an Entry Regarding Motion to Compel, which found that Lilly had not pled willful infringement in its Complaint. (Dk. # 96.) Lilly moved for reconsideration of the May 12, 2003 Order, or in the alternative, for leave to file an amended complaint. (Dk. # 105.) Teva opposed Lilly's motion and made a contingent motion to bifurcate the issue of willful infringement. (Dk. # 109, 110.) On November 3, 2003, the Court granted Lilly's contingent motion to amend its Complaint as well as Teva's contingent motion to bifurcate the issue of willful infringement. (Dk. # 182.)

Thus, the only remaining issues to be tried were Teva's invalidity defenses under 35 U.S.C. §§ 102 and103. The case was tried {*71} to the Court over a nine-day period between November 12 and November 24, 2003.

Conclusions of Law

The '998 patent is presumed to be valid under 35 U.S.C. § 282. **Jones v. Hardy, 727 F.2d 1524, 1528 (Fed. Cir. 1984)**. Teva, the party challenging the validity of the '998 patent, bears the burden of proving invalidity by clear and convincing evidence. **Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1282 (Fed. Cir. 2003)**. The Supreme Court has defined "clear and convincing" evidence as that which gives the finder of fact "an abiding conviction that the truth of [the proponent's] factual contentions are highly probable." **Colorado v. New Mexico, 467 U.S. 310, 316, 81 L. Ed. 2d 247, 104 S. Ct. 2433 (1983)**.

Where evidence of invalidity was before the patent examiner during prosecution, the challenger's burden is especially heavy; "he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with {*72} the level of skill in the art and whose duty it is to issue only valid patents." **McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1353 (Fed. Cir. 2001)** (internal citations omitted). However, where evidence concerning invalidity was not before the patent examiner during prosecution, no such deference is due with respect to evidence the examiner did not consider. **Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 714 (Fed. Cir. 1984)**.

§ 102--Anticipation

Teva argues that the '998 patent is invalid as anticipated under 35 U.S.C. § 102(b). A patent is invalid as anticipated if the claimed invention was "in public use or on sale in this country" or "described in a printed publication" at least one year before the effective filing date of the patent. In this case, the effective filing date of the '998 patent is October 22, 1987. A public use or prior art reference anticipates a patent claim if each and every limitation of that claim is found, either expressly or inherently, in that single public use or prior art reference. **Akamai Technologies, Inc. v. Cable & Wireless Internet Services, Inc., 344 F.3d 1186, 1192-93 (Fed. Cir. 2003)** {*73} (citing **Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576-77**

(**Fed. Cir. 1991**)). "The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference." **Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1368 (Fed. Cir. 2003)** (internal quotation marks and alterations omitted).

Teva contends that Claim 2 of the **'998 patent** was inherently anticipated by one or all of the following prior art references: the **'895 patent** (DTX A), the **'213 patent** (DTX WY), the Stark article (DTX GB), and the Cohn article (DTX AV). In addition, Teva asserts that Lilly's Fluoxetine Trials are an inherently anticipating public use of the technology claimed by the **'998 patent**. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." **Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1377-78 (Fed. Cir. 2001)**.

Lilly, however, argues that Teva's cited prior art references and alleged {*74} public use do not anticipate Claim 2 of the **'998 patent** because they do not disclose the use of fluoxetine for "the same purpose." Rather, the prior art references and alleged public use direct the use of fluoxetine to treat affective disorders, a purpose different from the treatment of PMS. Because PMS is linked to the menstrual cycle, PMS is distinguishable from affective disorders, including depression and anxiety. For example, only women suffer from PMS, and their symptoms are on-again, off-again in nature, depending upon the menstrual cycle. As a result of these differences, a symptom common to both PMS and depression, such as depressed mood, may require different treatment depending on the context in which it appears.

Specifically, Lilly contends that to anticipate a claim reciting the use of an agent to treat a particular disorder, the prior art must disclose the use of that agent with the *intent* or *purpose* of treating the claimed disorder, here PMS. **Rapoport v. Dement, 254 F.3d 1053 (Fed. Cir. 2001); Jansen v. Rexall Sundown, 342 F.3d 1329 (Fed. Cir. 2003)**. Teva, to the contrary, asserts that the authority relied upon by Lilly is factually {*75} distinguishable from this case.

The claim at issue in Jansen reads in pertinent part as follows:1. A method of *treating or preventing macrocytic-megaloblastic anemia* in humans which anemia is caused by . which comprises administering a daily oral dosage of a vitamin preparation *to a human in need thereof* comprising .**342 F.3d at 1330**. The Jansen court held that, as in Rapoport, "the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. . The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of intentional purpose for which the method must be performed." **342 F.3d at 1333**.

To compare, Claim 2 states:A method for *treating* disturbances of mood, disturbances of appetite, or both, *associated with pre-menstrual syndrome*, comprising administering *to a woman* prior to the onset of her menstrual period a composition {*76} consisting essentially of approximately 5 mg to 120 mg of fluoxetine."Teva argues that because Claim 2 "does not expressly limit treatment to individuals 'in need thereof,' the claim language 'a method for treating' should be construed as a 'statement of effect that may or may not be desired or appreciated.'" Teva Corrected Post-Trial Br. pp. 16-17.

Teva's argument, however, is incomplete. The Jansen court expressly declined to reach the situation we face here, one in which the "to a human in need thereof" phrase was not a part of the disputed claim. Jansen held only that the "to a human in need thereof" phrase *together with* the "treating or preventing" phrase required an intent to treat the specified condition. **342 F.3d at 1333**. Therefore, we must decide whether the "method for treating" phrase in the context of Claim 2 is sufficient to compel an intent to treat PMS.

Teva uses the prosecution history of **U.S. Patent No. 5,223,540** ("the **'540 patent**"), which issued from a later-filed application in the same chain as the **'998 patent**, to demonstrate the significance of the "human in need thereof" language. Teva contends that during prosecution, the patent {*77} examiner rejected a claim identical in form to Claim 2 of the **'998 patent** because the claim as written covered administration to "any woman." (DTX O p. 62). To address the examiner's concerns, the claim in the '540 application was amended to add the phrase "in need of such treatment." (DTX O pp. 75, 79). n17

---Footnotes---17

n17 The claim was amended as stated; however, we note that the examiner rejected the **'540** amendment on obviousness grounds, a decision that was overruled on appeal. (DTX O p. 116).

---End Footnotes---

In response to Teva's argument, Lilly refers to a subsequent amendment to the **'998 patent** itself. The examiner initially rejected the amendment in part because the claims drew on an open host, *i.e.*, a woman, which could read on the same host as the prior art administration. However, in response to this rejection, the attorney prosecuting the patent argued that "the woman referred to in the cited claims is a woman in whom the mood and/or appetite disturbances described would otherwise occur prior to the onset of menstruation {*78} . and possibly continue for several days . after onset of menstruction." The examiner found the argument convincing and allowed the claim. (DTX N pp. 110, 116). Teva's expert, Dr. Miller, confirmed Lilly's interpretation of Claim 2 to require an intent to treat PMS when she testified that Claim 2 covers only women with PMS, as that term was defined by the Court. (Miller Tr. p. 383.)

Therefore, we conclude, as Lilly does, that Claim 2 requires an intent to treat PMS. In order to demonstrate an intent to treat PMS, Claim 2 uses the phrase "associated with PMS" to modify the "disturbance" being treated instead of the phrase "in need thereof" to modify "a woman," the subject of the treatment. As such, the phrase "associated with PMS" in the preamble is "not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of intentional purpose for which the method must be performed." See **Jansen, 342 F.3d at 1333.**

All the experts agree that Teva's alleged public use and prior art references--the **'895 patent** (DTX A), the **'213 patent** (DTX WY), the Stark article (DTX GB), the Cohn article (DTX AV), and the Lilly Fluoxetine Trials--do {*79} not include an intent to treat PMS. (Miller Tr. 429, 433-39 (regarding the **'895** and **'213 patents** and the Stark and Cohn articles); Brown Tr. pp. 783-84 (regarding Stark article and clinical trials); Endicott Tr. pp. 1058-60, 1062 (regarding **'895** and **'213 patents** and Stark and Cohn articles)). Accordingly, we find that Teva has failed to prove anticipation by clear and convincing evidence.

Although not necessary to our holding, we address Teva's additional arguments of anticipation in turn and find that they, too, are unconvincing. Teva's proposed prior art references, the **'895 patent**, the **'213 patent**, the Stark article, and the Cohn article, do not even suggest the claimed therapeutic use (to treat a diagnosed case of PMS). See **Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1372 (Fed. Cir. 2003).** Nor do they limit the target of the treatment to women.

In addition, Teva cites Lilly's pre-October 22, 1986 Fluoxetine Trials as a public use inherently anticipating of each and every limitation of Claim 2. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. **MEHL/Biophile Intern. Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999)** {*80} (citing **In re King 801 F.2d 1324, 1326 (Fed. Cir. 1986)).** Recognition or appreciation of the newly-discovered necessary result by a person of ordinary skill in the art before the critical date is *not* required to show anticipation by inherency. **Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1377 (Fed. Cir. 2003).**

Teva argues by analogy to an August 4, 1988 office action in which the patent examiner of the **'998 patent** rejected pending claims in part on the basis that the prior use of a drug (d-fenfluramine) in clinical work would have inherently anticipated the pending claims. Dr. Bolton, Teva's statistical expert, testified that, during open label clinical trials, Lilly or its agents administered fluoxetine in dosages between 5 mg and 120 mg to at least 112 women between the ages of 18 and 45 who had been diagnosed with major depressive disorder. Dr. Bolton stated that, based on a 65 percent prevalence rate of premenstrual depression among women with major depressive disorder, there was a greater than 99.9999% certainty that one or more of these 112 women was suffering from disturbances of mood associated with PMS when she participated in the {*81} clinical trial.

For a number of reasons, however, Dr. Bolton's analysis of the clinical trial evidence does not establish anticipation. First, the August 4, 1988 office action took place approximately 15 years before the Federal Circuit's decisions in Rapaport and Jansen, which we found applied to this case to require an intent to treat PMS. All the experts agree that the purpose of Lilly's Fluoxetine Trials was to determine the effectiveness of fluoxetine in the treatment of major depressive disorder, not PMS.

Second, Dr. Bolton's analysis is not based on a single prior art reference. **Structural Rubber Prod. v. Park Rubber, 749 F.2d 707, 715 (Fed. Cir. 1984);** see also **Scripps Clinic & Research Foundation v. Genentech, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991)** ("If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not anticipation, but obviousness.") Rather, his calculations rely both on an examination of case report data and on 65 percent prevalence rate taken from the report of Teva's expert, Dr. Miller. (Bolton Tr. pp. 843, 851). Lilly challenges {*82} the accuracy of the prevalence rate chosen by Dr. Miller because it reflects the rate at which patients with major depressive disorder also had PMS at some point in their lifetime,

not simultaneously with the disorder. See Lilly's Reply Br. p. 12. Teva responds that the calculations would remain relatively unchanged even if Dr. Bolton used a hypothetical prevalence rate of ten percent.

To the extent that Teva maintains that the prevalence rate is irrelevant, we agree, but for a different reason. Dr. Bolton bases his testimony on probabilities--concededly, very strong probabilities, but probabilities nonetheless. A claim limitation is inherent in the prior art if it is necessarily present in the prior art, *not merely probably or possibly present.* **Rosco v. Mirror Lite, 304 F.3d 1373, 1380 (Fed. Cir. 2002)** (emphasis added). "Inherency . may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, {*83} " the prior art has anticipated the claim at issue. **Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991).**

Dr. Bolton's result is not a "necessary" or "natural" one. He could not identify any one patient record and say with certainty that any one female subject actually had PMS. **Contrast Proctor & Gamble Co. v. Nabisco Brands, Inc., 711 F. Supp. 759, 11 U.S.P.Q. 2d 1241, 1252-53 (D. Del. 1989)** (noting that defendant produced evidence that an employee of plaintiff produced the desired result following the claimed method on her first try). We find credible the experts' collective testimony that PMS requires a careful diagnosis, which to be confirmed must be charted over several menstrual cycles.

To supplement Dr. Bolton's statistical analysis, Teva offers the testimony of Dr. Brown to show that a patient record from Lilly's pre-October 1986 Fluoxetine Trials anticipated Claim 2. Dr. Brown testified that: (1) the subject woman suffered from disturbances of mood associated with PMS, and (2) both she and her physician appreciated that the fluoxetine she received in the clinical trial ameliorated those disturbances. This characterization {*84} misstates the facts, however.

In week 5 of the double-blind trial, the patient complained of "premenstrual tension," which abated as of week 6. Such an anecdotal comment is insufficient to diagnose PMS, however. Even Dr. Brown acknowledged that the patient was not given a thorough evaluation (*i.e.*, no documentation of the start of menses exists) and that frequently women erroneously attribute symptoms to PMS. Based on the structure of the clinical trial, we were able to determine that the patient was taking fluoxetine during the blinded portion of the trial. Depending on the length of the placebo lead-in period, by her fifth visit, she would have been taking fluoxetine for at least a week. Fluoxetine relieves symptoms of PMS within a day, but takes two to three weeks to relieve symptoms of depression. Therefore, we conclude that the patient did not suffer from disturbances of mood or disturbances of appetite associated with PMS.

The evidence as presented does not convincingly demonstrate a use of the method claimed in the **'998 patent**--the treatment of PMS. Nevertheless, Teva maintains that Lilly's Fluoxetine Trials constitute a "public use" under **§ 102**. The statutory phrase {*85} "public use" does not mean open and visible in the ordinary sense. Rather, it includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction, or obligation of secrecy to the inventor. **New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1297 (Fed. Cir. 2002)** (citations omitted). Because the inventors named on the **'998 patent** are Richard and Judith Wurtman, who were affiliated with MIT, and Lilly did not sublicense the **'998 patent** until 1997, almost a decade after the clinical trials at issue were completed, Teva contends that Lilly should therefore be considered a person other than the inventor who used the claimed invention.

We see at least two problems with Teva's contention. First, because Lilly's Fluoxetine Trials did not practice the claimed method, the use of fluoxetine to treat PMS, they do not constitute a "use" of the claimed invention, public or private. **Contrast SmithKline Beecham Corp. v. Apotex Corp., 365 F.3d 1306, 1318 (Fed. Cir. 2004)** (concluding that where the claim covered the compound regardless of its use as an antidepressant, the clinical tests, which measured the {*86} efficacy and safety of the compound as an antidepressant, did not constitute an experimental use of the claimed invention, and thus that the use was public). In addition, unlike the clinical trial records in **SmithKline,** both Lilly and the Fluoxetine Trial investigators were required to maintain the confidentiality of their records. Therefore, during the prosecution of the **'998 patent** from 1987 to 1990, the Wurtmans and MIT would not have had access to the clinical trial records and could not have disclosed them to the patent examiner. In any event, we conclude the absence of the Fluoxetine Trial records is not material given the examiner's citations to the '895 and '213 patents. He would likely have been aware of Lilly's use of fluoxetine to treat depression during the prosecution of the **'998 patent.** (DTX M p. 253).

Because Teva has not demonstrated that the alleged prior art references require an intent to treat PMS (or

even suggest such a therapeutic use), and because Teva has not established that Lilly's Fluoxetine Trials constitute a public use inherently anticipating each and every limitation of Claim 2, Teva has not proven by clear and convincing evidence that the '998 patent {*87} is anticipated under § 102.

§ 103--Obviousness

A patent claim is invalid under 35 U.S.C. § 103(a) "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The ultimate determination of whether an invention would have been obvious under § 103(a) is a legal conclusion based on underlying findings of fact. **Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003)** (citing **In re Kotzab, 217 F.3d 1365, 1369 (Fed. Cir. 2000)**). The underlying factual inquiries include (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art.Id. (citing **Graham v. John Deere Co., 383 U.S. 1, 17, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966)**). In addition, where offered, the court must also consider a fourth factor, objective indicia of nonobviousness. **Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000)**. {*88}

If all the elements of an invention are found in a combination of prior art references, a proper analysis under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they carry out the claimed process; and (2) whether the prior art would also have revealed that in so carrying it out, those of ordinary skill would have a reasonable expectation of success. **Velander, 348 F.3d at 1363** (citing **In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991)**, and **In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)**). This reasonable expectation of success does not require a showing of "absolute predictability." **Yamanouchi, 231 F.3d at 1343**. Whether a motivation to combine prior art references has been demonstrated is a question of fact. **Winner International Royalty Corp. v. Wang, 202 F.3d 1340, 1348 (Fed. Cir. 2000)**. Both the motivation to combine references and the reasonable expectation of success must be founded in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be {*89} solved. **Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000)**. They may not, however, be taken from the applicant's disclosure." **Velander, 348 F.3d at 1363**.

A. Scope and content of prior art

The obviousness of a claimed invention under § 103 must be assessed as of the "date of invention." The date of invention is deemed to be the date on which the inventor filed its patent application, the "constructive reduction to practice," unless the inventor furnishes sufficient proof of an earlier "conception" and "actual reduction to practice." See **Kridl v. McCormick, 105 F.3d 1446, 1449-50 (Fed. Cir. 1997)**; see also **Brown v. Barbacid, 276 F.3d 1327, 1339 (Fed. Cir. 2002)**. "Conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is therefore to be applied in practice. Conception must include every feature or limitation of the claimed invention. **Kridl, 105 F.3d at 1449-50** (citations omitted). An actual reduction to practice requires a determination that the inventor's conception, {*90} including all its limitations, will work for its intended purpose. **Cooper v. Goldfarb, 154 F.3d 1321, 1327-28 (Fed. Cir. 1998)**.

"Conception must be proved by corroborating evidence which shows that the inventor disclosed to others his complete thought expressed in such clear terms as to enable those skilled in the art to make the invention." **Kridl, 105 F.3d at 1449-50** (citations omitted). Similarly, in order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence. **Cooper, 154 F.3d at 1330**. The inventor's own statements and documents are not enough. **Hahn v. Wong, 892 F.2d 1028, 1032 (Fed. Cir. 1989)**.

In this case, the filing date of the '998 patent is October 22, 1987. The only evidence Lilly offers to support an earlier date of invention is the testimony of the inventor, Dr. Richard Wurtman. Lilly does not produce any document or witness testimony to corroborate his testimony. Dr. Judith Wurtman, a co-inventor, was not involved with the fluoxetine study; she did not see the results except as they were presented in the '998 patent. Therefore, in the absence {*91} of sufficient proof of an earlier conception and actual reduction to practice, we must conclude that the date of invention is the filing date of the '998 patent, October 22, 1987. Accordingly, the relevant prior art consists of those references dated one year or more before the date of invention. In this case, that date is October 22, 1986. See **Scripps Clinic & Research Foundation, 927 F.2d at 1576-77**.

Next, we must determine what the prior art had taught about fluoxetine as of the filing of the '998 patent.

Although fluoxetine was not on the market in the United States, it was available in Europe as of November 1986. Clinical trials involving fluoxetine and the nature of the drug itself had also been described in the scientific literature.

In its obviousness argument, Teva again relies on the prior art discussed in our anticipation analysis, among other references. The **'895 patent**, which was filed in September 1975 and issued in April 1977, teaches that fluoxetine is an effective treatment of depression in humans. Similarly, the **'213 patent**, which was filed in 1983 and issued in 1986, establishes that fluoxetine is an effective treatment of anxiety in humans. In {*92} separate articles in March 1985, Cohn and Stark tested the efficacy of fluoxetine and found that fluoxetine relieved the symptoms of depression signifieantly better than placebo and that it caused fewer and less severe side effects than another antidepressant, impramine. n18 These prior art references teach all but one, key element of the **'998 patent**--that fluoxetine is an effective treatment of symptoms *associated with PMS*.

- - -Footnotes- - -18

n18 Other publications of the same era support these findings. For example, in December 1986, Benfield *et al* published a drug evaluation, which stated that fluoxetine was known to be a SSRI, and therefore, to be effective in treating conditions caused by serotonergic deficiencies, including depression. (Miller Tr. pp. 250-51; DTX AC pp. 482-83). Benfield also discussed fluoxetine's side effect profile, which improved upon that of tricyclic antidepressants. Id. p. 484. This reference was published after October 1986, but it was before the patent examiner during the prosecution of the **'998 patent**.

- - -End Footnotes- - -

{*93} In order to determine whether one of ordinary skill in the art would have thought it obvious to use fluoxetine to treat PMS, we must first establish what was known about PMS as of October 22, 1987. The answer is not much. There were many theories as to the cause of PMS, but none had been definitively proven. In 1985, after having surveyed the many theories as to the etiology of PMS, Janowsky stated that "no existing hypothesis of PMT [premenstrual tension syndrome] is even close to being proved at this time." (DTX CQ p. 7). While a leading theory in 1987 was one related to sex hormone changes (*i.e.*, progesterone) linked to a woman's menstrual period, many other theories were being tested. Another theory, which will be discussed below, was serotonin deficiency.

In considering whether one of ordinary skill in the art would have been motivated to use fluoxetine, an effective treatment of depression, to treat PMS, we note as of October 1987, the nature of the relationship between PMS and affective disorders was still being explored. PMS is not a subset of depression, which is itself a stand alone affective disorder. Depression in the sense of depressed mood, however, may be a symptom {*94} of PMS. There are significant differences between PMS and affective disorders such as depression or anxiety. PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. PMS affects only women whereas both men and women suffer from depression. PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may awake early in the morning and lack interest in the world around them, and not all PMS patients are depressed). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

As of October 1987, those skilled in the art were just beginning to look past these differences to discover the relationship between affective disorders and PMS. In February 1985, Janowsky suggested in a journal editorial that "[a] logical strategy for studying [premenstrual tension syndrome ("PMT")] may be to assume that {*95} the same neurotransmitter and neuromodulators thought to regulate affective disorders are those which also modulate PMT." (DTX CQ p. 5). See also DTX GX (March 1979) p. 361 ("Lowered levels of serotonin . have consistently been associated with depressive states. Thus, one would predict depression just prior to menstruation, with some effect continuing for about a week."). Also, in a November 1985 journal article, DeJong, *et. al.*, stated that "the results of several studies suggest that a special relationship exists between premenstrual syndromes and major psychiatric disorders, particularly affective illness." (DTX BC p. 1359). n19

- - -Footnotes- - -19

n19 None of these prior art references were in front of the patent examiner during the prosecution of the **'998 patent**. However,

the theories proposed by these references are very similar to the serotonin hypothesis Rapkin tested in her 1987 article, which was before the patent examiner.

- - -End Footnotes- - -

Also in the early 1980s, clinical researchers attempted to measure the serotonin functioning {*96} in women with PMS to determine if a serotonin deficiency caused PMS. In 1984, Taylor studied the correlation between the severity of a woman's PMS and the decrease in that woman's peripheral serotonin levels. Building on Taylor's findings, in a study published in October 1987, Rapkin compared women with PMS to asymptomatic women and found that women with PMS had lower serotonin levels throughout the menstrual cycle.

Lilly's expert witness, Dr. Blier, tried to discredit Taylor's study by arguing that she did not have a control group of asymptomatic women. In addition, Dr. Blier challenged Rapkin's findings by showing that (1) she did not control for diet, which was known in 1987 to affect serotonin, (2) blood serotonin levels of women with PMS did not change during the menstrual cycle, and (3) although blood platelets model serotonin neurons in the brain, changes in serotonin levels in the blood do not indicate the same type of activity in the brain.

Although we credit Dr. Blier's testimony as to the mechanics of serotonin functioning and note his criticisms of the Taylor and Rapkin articles, Drs. Taylor and Rapkin are not on trial here. Substantial evidence exists that those of ordinary {*97} skill in the art relied, at least in part, on Taylor and/or Rapkin, including the authors of the DSM-IV, who derived the definition of PMDD followed by the American Psychiatric Association. In determining obviousness, references are read not in isolation but for what they fairly teach in combination with the prior art as a whole. **In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986)**. Together, these references support the involvement of serotonin with PMS, but it ends there. Neither doctor conducted a clinical trial of any drug, including fluoxetine. Furthermore, Rapkin specifically states that as of 1987 further studies were necessary "to elucidate the association between diminished peripheral serotonin and premenstrual syndrome." (DTX FF p. 537).

Although the serotonin hypothesis was gaining ground, it was still one theory among many. In Janowsky's 1985 article, he noted that researchers had tried to correlate changes in the menstrual cycle with changes in everything from hormones (e.g., estrogen, progesterone, prolactin, mineralocorticoids and adrenocortical hormones), to electrolytes, to neurotransmitters (e.g., opioid polypeptides, cholinergic mechanisms, to {*98} catecholamine alterations, and serotonin), to somatic parameters. (DTX CQ pp. 3-6).

Given the uncertainty surrounding the cause of PMS, we next determine how one of ordinary skill in the art would have approached treating the syndrome. The parties devoted much energy in their briefing to the extent to which PMS was treated symptomatically in 1987, too much in our view. Doctors treating a patient presenting with PMS would have been motivated to seek treatment for the disorder as a whole. However, because the etiology of PMS was and is not known, doctors would most likely have had to target predominant or groups of symptoms for treatment. In 1982, O'Brien discusses the need for individualized assessment because of the wide variety of symptoms with which patients present. He then suggests that physicians treat their patients first with oral contraceptives or progestagen, and then, if neither of those options is effective, physicians should "determine the most distressing symptom or symptom type." (DTX DP pp. 147-48).

If depression was the predominant symptom, the experts counseled caution. O'Brien found that, in general, "psychoactive drugs do not play an important role in treating {*99} the premenstrual syndrome." (DTX DP pp. 142, 148). As of Keye's November 1985 article, "adequate trials of [MAO] inhibitors [and] of tricyclic antidepressant in premenstrual syndrome have not yet been reported. . While psychoactive drugs may relieve a selected premenstrual symptom such as depression or anxiety, none would appear to be broad enough in its effect to provide satisfactory relief for women with severe and multiple symptoms." (DTX CU pp. 483-84). Furthermore, the relief available from the antidepressants available at the time, tricyclic antidepressants and MAO Inhbitiors, had to be weighed against the unpleasant side effects. For example, such risks and side effects include risk of suicide with tricyclics (PTX 10 at 2627), drug interactions with MAOIs (PTX 10 at 2563), and lithium toxicity with lithium. ACOG did not recommend treatment of PMS with antidepressants until 1995.

Another treatment which was known to relieve, at least in part, the mood symptoms of PMS was alprazolam, which is an anti-anxiety agent. However, alprazolam has harmful side effects such as palpitations, tremors and seizures. Additionally, physicians were not particularly comfortable using

alprazolam {*100} to treat PMS in part because it was addictive.

Proponents of the serotonin hypothesis recommended testing agents that influence the serotoninergic pathway, namely tryptophan, chlorimipramine, and trazodone hydrochloride. As of October 1987, however, tryptophan had been shown, by Dr. Endicott, to be ineffective agent for the treatment of PMS. Noticeably, no one suggested the use of fluoxetine or fenfluramine, two known serotoninergic enhancing agents, to treat PMS before the Wurtmans. Given the available treatment options, fluoxetine, with its high level of effectiveness and improved side effect profile, understandably was a "therapeutic triumph." (Brown Tr. p. 774).

B. Level of ordinary skill in the prior art

The parties dispute the appropriate level of ordinary skill in the art. Lilly argues that the one of ordinary skill in the art is a community-based OB/GYN or family practitioner. Teva, by contrast, contends that "the person of ordinary skill in the art must be an individual who, in the October 1987 time frame, would have been seeking to find a medication that would be effective in treating the specific PMS symptoms listed in claim 2 of the **'998 patent**-disturbances {*101} of mood and/or appetite." Teva Corrected Post-Trial Br. p. 24. The Federal Circuit teaches that factors pertinent to ascertaining the theoretical ordinary level of skill in the art are: (i) the inventor's educational background; (ii) the kinds of problems confronted in the art; (iii) solutions found previously; (iv) the speed of innovation in the art; (v) the level of sophistication of the technology; and (vi) the educational level of active workers in the field. **Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983).**

In this case, the Wurtmans, who were the inventors of the **'998 patent**, were clinical researchers interested in using serotoninergic drugs to alleviate a constellation of symptoms associated with PMS. Dr. Richard Wurtman has an M.D. and Dr. Judith Wurtman has a Ph.D. in cell biology. As explicated above, in October 1987, although many theories existed as to the cause and treatment of PMS, none was generally accepted. During the prosecution of the **'998 patent**, the art, including the theory of serotonin deficiency, was continuously evolving. The "educational level of active workers in the field" varied. Those active in the development {*102} of new drug therapies, such as clinical researchers like the Wurtmans, read academic literature and conducted experimental clinical trials. However, community-based physicians, whether OB/GYNs, family practice physicians or psychiatrists, ordinarily did not.

In this context, we conclude that a community-based physician would not be one of ordinary skill in the art because, as Dr. Endicott acknowledged, community-based physicians, on average, not only do not conduct independent research or seek patents, but they also do not read academic literature. If a person is not generally aware of the relevant prior art, he or she cannot be considered someone of ordinary skill in that art. Yet, to limit "one of ordinary skill in the art" to clinical researchers would be too restrictive. Therefore, in our view, one of ordinary skill in the art is a hypothetical medical doctor (an OB/GYN, a family practice physician, or a psychiatrist) who: (1) regularly sees and treats patients suffering from PMS, and (2) is familiar with the relevant prior art. See **Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 352 (D. Del. 1991)** (finding that where the patent was directed {*103} to the development of beta-blockers for the treatment of hypertension, "the person of ordinary skill in the art would be an individual with a PhD degree in organic chemistry, with an emphasis in medicinal chemistry ., who would have some experience with the development of beta-blockers, and would be thoroughly familiar with the prior art which discusses the structure-activity relationships of the existing beta-blockers and have knowledge of the methodologies of drug development").

C. Differences between the claimed invention and the prior art

From the prior art, as of October 1987, one of ordinary skill would have known that: (1) fluoxetine is an effective treatment of anxiety and depression in humans; (2) fluoxetine is effective because it inhibits serotonin reuptake by the neuron, thereby preventing or lessening the serotonergic deficiencies that cause depression and anxiety; (3) although depressed mood is a symptom of PMS, PMS is a condition wholly distinct from depression; (4) the etiology of PMS is unknown; (5) numerous theories exist as to the cause of PMS, one of which suggests that PMS is related to serotoninergic functioning; and (6) there was not a drug {*104} therapy available to treat PMS as a whole. To learn all of this information, however, one would have to survey prior art references numbering well into the double digits. Even then, one would not find a single references suggesting the use of fluoxetine to treat PMS.

We are very wary of using hindsight as a blueprint of our obviousness analysis. n20 The Federal Circuit has made clear that "the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references."

Ecolochem, 227 F.3d 1361, 1371-72. As stated above, such a suggestion to combine references may be founded in the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. **Brown & Williamson, 229 F.3d at 1125.** We note, too, that although the number of references used is not determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

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n20 Teva encourages us to consider the Wurtmans' own prior art (the '445, '815 and '161 **patents** as well as DTX XI, a volume in the Annals of the New York Academy of Sciences edited by the Wurtmans and dated July 1987) as evidence of the obviousness of the **'998 patent.** This prior art suggests that serotonin regulates carbohydrate intake in patients with either CCO or SAD. Teva argues that given this knowledge, one of ordinary skill in the art would have discovered that serotonin regulates disturbances of appetite associated with PMS. However, no one connected serotonin and carbohydrate regulation with PMS, or taught the use of fenfluramine or fluoxetine to treat PMS, before the Wurtmans. Teva's reasoning would use the Wurtmans' innovations against them and constitute just the kind of connect-the-dots hindsight analysis the Federal Circuit counsels against.

---End Footnotes---

{*105} There is no suggestion of combining references in the prior art. In 1987, the hypothesis that a serotonin deficiency caused PMS was barely acknowledged, and thus, not compelling. With regard to Rapkin's 1987 article, the Wurtmans would not likely have relied on it because it went to print in the same month as they filed the **'998 patent.** At most, the prior art references invited those of ordinary skill in the art to explore further the relationship of serotonin to PMS. See **Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).** There was no indication in the prior art, however, that an agent thought to affect serotonin was an effective treatment for PMS. Contrast **Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1484-85 (Fed. Cir. 1997)** ("The prior art combinations of an analgesic [other than that proposed in the patent at issue] and a decongestant in a single unit dosage were known to be particularly effective for treating sinus headaches."). In fact, tryptophan, an agent thought to influence the serotoninergic pathway, was shown to be completely ineffective in the treatment of PMS. Moreover, the prior art demonstrated {*106} that anti-depressants as a class were an incomplete treatment of PMS.

Given that there was no known cause or treatment of PMS, the nature of the problem to be solved may have created a "can't hurt to try" attitude in the mind of those of ordinary skill in the art. See **Pro-Mold and Tool Co., Inc. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573 (Fed. Cir. 1996)** ("Suggestion to combine references 'may also come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem.'") (citations omitted). Considering that the need for an effective treatment was so great, that the symptoms of PMS and depression were similar, that the serotonin hypothesis was slowly gaining recognition, and that the side effects of fluoxetine were known to be mild as compared to other anti-depressants and anti-anxiety agents on the market in October 1987, perhaps in hindsight it would have been "obvious to try" fluoxetine to treat PMS. "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure {*107} itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." **Gillette Co. v. S.C. Johnson, 919 F.2d 720, 725 (Fed. Cir. 1990)** (internal citations omitted). However, "obvious to try" is not the standard in a **§ 103** obviousness inquiry. **Ecolochem, 227 F.3d at 1374.** Teva must point to "the specific sources of the motivation to combine prior art references" in order to prevail on this theory. Id.

Our considered judgment is that Teva has not provided clear and convincing evidence of a motivation to combine references. History has shown that not even those with extraordinary skill in the art and unfettered access to fluoxetine, clinical researchers at Lilly, for example, were motivated to treat PMS with fluoxetine prior to the Wurtmans.

One of ordinary skill in the art must also have a reasonable expectation of success, which we find also lacking here. In 1987, scant information was known about the etiology of PMS. Any new method of treatment that proved to be effective would have been unexpected, and like fluoxetine, a "therapeutic triumph." In {*108} sum, we conclude that Teva has

failed to produce clear and convincing evidence that "a skilled artisan confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." **In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998).**

D. Objective indicia of nonobviousness

Our primary finding of nonobviousness is buttressed by secondary indicia of nonobviousness. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached. **Minnesota Min. and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1573 (Fed. Cir. 1992).** "Evidence of secondary considerations may often be the most probative and cogent evidence in the record." **Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983).** Lilly offers many alleged objective indicia of nonobviousness for our consideration.

1. Commercial success

With regard to commercial success, Lilly, the patentee, bears the burden {*109} of proving a "nexus," or a legally and factually sufficient connection between the proven commercial success and the patented invention. **Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988).** The Federal Circuit has held that "a presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.'" **Ecolochem, 227 F.3d at 1377.** Once Lilly makes the requisite showing of nexus between commercial success and the patented invention, the burden shifts to Teva to prove that the commercial success was instead due to other factors extraneous to the patented invention. Id.

Lilly has satisfied its burden by offering evidence that Sarafem, its product covered by Claim 2 of the '998 patent, had sales of $ 176.2 million from August 2000 to December 2002 and was the most prescribed product for the treatment of severe PMS during that time. See **Tec Air, Inc. v. Denso Mfg. Mich., Inc., 192 F.3d 1353, 1361 (Fed. Cir. 1999)** {*110} (providing that sales figures coupled with market data provide stronger evidence of commercial success than sales figures alone). As evidence of its market share, Lilly also produced Sarafem's prescription data.

Even though a competitor, Zoloft, entered the PMDD market in May 2002, total prescriptions of Sarafem declined only slightly from 2001 to 2002. Repeat prescriptions, which Lilly's expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 as compared to 2001 and remained stable with a slight decline through 2002. Teva's expert, Dr. Schmittlein, opined that new prescriptions, not repeat prescriptions, are the most important indicators of future product success because they demonstrate whether physicians view the product as continuing to play an important role in their treatment practice. However, new prescriptions, too, remained stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). Although Zoloft's appearance on the scene no doubt diverted some new prescriptions from Sarafem, Sarafem remained the market leader.

{*111} Teva disputes even the presumption that Sarafem achieved "significant sales in a relevant market." Teva argues that Sarafem was not a successful product "by Lilly's standards" because sales of Sarafem did not meet Lilly's projections. Teva also offers expert evidence that Sarafem sales in its market did not mirror the sales of Prozac in its market and that Lilly did not think it worthwhile to continue a "$ 300 million type of product" like Sarafem. We find Teva's arguments largely beside the point and unpersuasive. Sales of Prozac were by every measure extraordinary, which make them an unreliable benchmark for commercial success. In addition, that Lilly, an international pharmaceutical company, might seek to divest itself of a "$ 300 million product" more likely reflects that company's internal strategic goals rather than an indication that Sarafem would not be "a commercial success" for another, smaller company. See **Eli Lilly and Co. v. Zenith Goldline Pharms., Inc., 2001 U.S. Dist. LEXIS 18361 (S.D. Ind. 2001)** ("if the patented drug were not a commercial success, generic manufacturers would have little interest in offering their own versions of the drug"). In fact, {*112} the patent certification letter that Teva sent Lilly on February 19, 2002, declared Sarafem to be a "commercially successful product" due in large part to the fact that "physicians felt comfortable prescribing Sarafem for PMS because of their familiarity with prescribing Prozac for depression." (PTX 98 at p. 9.)

Having demonstrated commercial success, Lilly shifts the burden to Teva to prove that the commercial success was due to factors extraneous to the patented invention. In addition, Teva contends that whatever success Sarafem did have was attributable to Lilly's marketing efforts, and that in the absence of any marketing and advertising, the sales of Sarafem would

have dropped to near zero by 2005. **In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996)** (explaining that "success is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention--as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter"). Teva offers much data to describe Lilly's marketing expenditures for Sarafem. For example, Teva asserts that approximately 80 percent {*113} of Lilly's "development costs" consisted of marketing expenditures. Importantly, however, Teva does not identify a drug with comparable economic performance to Sarafem permitting us to understand these marketing expenditures in context. Considering that much of Sarafem's product development would have been coincident with the development of Prozac, spending 80 percent of development costs on marketing may not have been inappropriate. We also question the basis for the near-zero sales figure (*i.e.*, what were the author's assumptions) and the effect the absence of advertising would have had on the sales of a comparable drug. This evidence notwithstanding, prescriptions of Sarafem remained relatively stable from 2001 to 2002, even though Lilly ended its direct-to-consumer marketing campaign in April 2001 and decreased its sales force from 1700 representatives in 2001 to 1020 in 2002. From this we believe that Sarafem's commercial success derived from the merits of the drug rather than the marketing activities by Lilly.

As additional evidence of nonobviousness, Lilly offers evidence that on June 19, 1997, Lilly sublicensed the **'998 patent** from Interneuron (the "1997 License"). Teva {*114} contends that this sublicense is not an objective indicator of nonobviousness for at least two reasons: (1) Lilly did not expect actually to have to pay running royalty rates in the amounts stated in the license (5% and 20%), and (2) Lilly had an incentive to license the **'998 patent** even if Lilly believed it to be invalid. We need not sort out the intricacies of the parties' experts' calculations of an effective royalty rate, however, because we accept Teva's contention that Lilly would have had an incentive to license the **'998 patent**, regardless of its validity.

We emphasize that in our view the licenses are a neutral factor. Substantial evidence exists that Lilly respected the validity of the **'998 patent** before licensing it, and licensed it because Lilly believed the treatment of PMS with fluoxetine would be a commercial success. For example, in 1992, when Drs. Stone and Brown applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. In addition, Dr. Tollefson, Vice-President with Eli Lilly Research Laboratories, testified that Lilly licensed the patent {*115} in 1997 because, convinced of the safety and efficacy of the use of fluoxetine to treat PMS, the company had decided to pursue commercial opportunities in that market.

Nonetheless, we find credible the testimony of Teva's expert, Mr. Gould, to the effect that, generally speaking, there are two reasons for a company to take a license: (1) for defensive purposes, to prevent it from being sued as an infringer by the patentee; or (2) for offensive purposes, to prevent others from entering the marketplace. Obviously, Lilly could use the license offensively whether or not it believed the license to be valid. Once Lilly licensed the **'998 patent**, Lilly could list it in the Orange Book with respect to Sarafem. Lilly then would have standing to bring suit for infringement against a generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months. The estimated sales value to Lilly of being the exclusive marketer of Sarafem was about $ 580,000,000. (Gould Tr. pp. 1018-23). Thus, while the 1997 license had considerable value to Lilly, it is not necessarily evidence of nonobviousness.

Ultimately, we find that Sarafem was a commercial success and as such, this factor {*116} weighs in favor of nonobviousness.

2. Long-Felt Need / Failure of Others / Simultaneous Invention n21

---Footnotes---21

n21 Lilly encourages us to consider Teva's "copying" of Sarafem as secondary evidence of nonobviousness. However, because the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, Teva's demonstration of equivalency of Sarafem to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention.

---End Footnotes---

Lilly asserts that, as of October 1987, there was a widespread failure of others to develop a safe and effective treatment for patients suffering from PMS. As established above, many hypotheses existed as to the etiology of PMS, but no known treatments had been devised or developed that provided relief to both the physical and emotional symptoms of PMS. Fluoxetine was the first drug to provide relief for both

kinds of symptoms, and the '998 patent was the first indication that fluoxetine was effective for PMS. Teva, {*117} by contrast, contends that the long-felt need that existed was simply for a serotoninergic drug with fewer side effects, and that the discovery of the fluoxetine molecule itself, in the form of Prozac, satisfied this need. Teva's contention, however, fails to account for the specific need to treat PMS. The identification of fluoxetine as an effective treatment of PMS did not occur until the '998 patent.

Next, Teva argues that others of ordinary skill in the art not only did not fail to develop the patented technology, but they also discovered it simultaneously with the Wurtmans. n22 Teva offers two clinical study protocols, Harrison, et al.'s *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study* dated February 5, 1988, and Stone, et al.'s *Assessment of Fluoxetine in the Treatment of Premenstrual Syndrome* dated July 12, 1988, to establish simultaneous invention. n23

- - -Footnotes- - -22

n22 Teva stresses the unlikelihood of Dr. Richard Wurtman's story of invention. We, however, find him credible. While we agree with Teva that Dr. Wurtman's version of events cannot establish an earlier date of invention than the filing of the '998 patent, Teva noticeably fails to identify any effect of the alleged surreptitiousness of Dr. Wurtman's actions on the validity of the '998 patent. The patent examiner was as aware of Dr. Wurtman's work as we are. See also, infra, note 7.

{*118} 23

n23 As explained, infra, note 11, Teva's other evidence of simultaneous invention is either irrelevant because it is hearsay or is dated after the Wurtmans and the Stone group had publicized their findings of fluoxetine's efficacy in treating PMS. Therefore, we do not consider it.

- - -End Footnotes- - -

With respect to simultaneous invention, "evidence of independent development of a patented device is indicative of obviousness if the circumstances of the development are shown to be similar to the state of the art when the patent was filed." **Pratt & Whitney Canada, Inc. v. U.S., 17 Cl. Ct. 777, 787 (Cl. Ct. 1989)** (citing **Stewart-Warner Corp. v. Pontiac, 767 F.2d 1563, 1570 (Fed. Cir.1985)**). Before we discuss the specifics of Teva's prior art references, we note the subtle change in the state of the art that occurred after the filing of the '998 patent in October 1987 and before the conception of any of these references stemming from the fact that, in January 1988, the FDA approved fluoxetine (Prozac) for the treatment of depression.

Although Teva asserts that before the FDA approved {*119} fluoxetine Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS, Teva does not support this allegation with any corroborative evidence. In all of the voluminous exhibits which the parties have introduced into evidence, we find no request dated before the filing of the '998 patent from a clinician to Lilly asking Lilly for fluoxetine to permit the study of the treatment of PMS, or any letter from Lilly to any clinician denying him or her the same. In fact, when Dr. Brown proposed his study to Lilly in 1988, Lilly agreed to fund it even though Lilly indicated that it would not be seeking an indication for fluoxetine in the treatment of PMS.

In addition, Teva argues that the motivation to treat PMS with fluoxetine was provided by the impending FDA approval of the drug. See **Richardson-Vicks, 122 F.3d at 1484**. In Richardson-Vicks, numerous prior art publications indicated that the FDA would likely approve dosages of the claimed drug, ibuprofen, in range of the claimed invention. The motivation to substitute ibuprofen for other analgesics in the prior art was particularly strong among ibuprofen manufacturers {*120} because it would allow them to strengthen the name brand recognition. Id. Here, however, there was no effective treatment of PMS for which to substitute fluoxetine, and the prior art references hailing the effectiveness of fluoxetine in treating depression didn't mention PMS. Therefore, we find no basis to hold that FDA approval impacted the filing of the '998 patent.

Next, we evaluate Teva's offerings of "contemporaneous development." The Federal Circuit has noted that simultaneous development may or may not be indicative of obviousness. **Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1460 (Fed. Cir. 1984)**. Evidence of contemporaneous development that occurs after the date of the patented invention, however, will almost never be probative of the ultimate conclusion of obviousness. See **Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 n. 4 (Fed. Cir. 1986)** (contemporaneous development more than a year after the filing date of patent is "of little probative value").

Approximately four months after the filing of the '998 patent, the Harrison group proposed the use of fluoxetine to treat the premenstrual {*121} exacerbation of chronic mild depression. About nine months after the filing of the '998 patent, the Stone group proposed a study of fluoxetine in the treatment of PMS. Because there is no symptom-free period, the Harrison group's protocol did not address PMS specifically, although its motivations for using fluoxetine were approximately the same as the Stone group's: patients with premenstrual depression had symptoms related to affective disorders, fluoxetine was known to increase serotoninergic function in the brain, fluoxetine had advantages over the then-existing antidepressants because it could address the increased appetite and sleep often found in patients with PMS, and fluoxetine had a low incidence of side effects, which is more appropriate for women who are asymptomatic 50-75% of the time.

These research clinicians, however, are persons of extraordinary skill in the art, and thus, their discoveries are irrelevant to a § 103 obviousness analysis. Although it appears that at least one member from each team met the criteria of one of ordinary skill in the art (*i.e.*, he or she was a physician who both treats patients and is familiar with the relevant literature), it is also {*122} true that these teams were comprised of research clinicians and that at least one member of each team participated in Lilly's clinical trials of fluoxetine to treat major depressive disorder. Therefore, both the Harrison group and the Stone group were much more familiar with fluoxetine specifically than one of ordinary skill in the art would have been. n24 While the evidence relied on by the researchers may have been available to the person of ordinary skill in the art as of 1987, he or she would not have weighed the possible treatment options with a eye on fluoxetine.

- - -Footnotes- - -24

n24 We do not mean to suggest that, at that time, anyone at Lilly suggested the use of fluoxetine to treat PMS. Such speculation on the part of Lilly's counsel is not supported by the evidence.

- - -End Footnotes- - -

Even if we were to consider this evidence, it supports only an "obvious to try" theory. Although Dr. Brown testified that "there was more than a reasonable expectation" of success that fluoxetine would be an effective treatment of PMS, Dr. Richard Wurtman {*123} testified that at the time he conducted his case study of fluoxetine, he did not know what to expect. In addition, other clinical researchers like Dr. Endicott undertook similar studies of other proposed PMS therapies and were met with disappointment. Finally, we note that the Stone group chose to study fluoxetine only after first considering progesterone. And, at about the same time as the Harrison group was conducting its fluoxetine study, it was also looking at the treatment of premenstrual depression with nortriptyline. Therefore, even those of extraordinary skill in the art had to hedge their bets.

Although we are not persuaded by Teva's assertions of simultaneous invention, even if we were to be, "the virtually simultaneous making of the same invention does not in itself preclude patentability of that invention." **Environmental Designs, Ltd v. Union Oil Co. of Cal., 713 F.2d 693, 698 n. 7 (Fed. Cir. 1983).** Assuming *arguendo* that Teva did establish a simultaneous invention, we conclude that it would merely counterbalance the other secondary indicia of nonobviousness (commercial success, failure of others, long-felt need and unexpected results). It would not {*124} outweigh our primary finding that, in 1987, the technology claimed in the '998 patent would not have been obvious to one of ordinary skill in the art.

Conclusion

For the reasons explained above, we hold that Teva has failed to prove by clear and convincing evidence that the '998 patent was invalid as anticipated under 35 U.S.C. § 102 or as obvious under 35 U.S.C. § 103. Accordingly, the '998 patent is valid and enforceable. n25

- - -Footnotes- - -25

n25 The only remaining issue still before the court is Lilly's claim of willful infringement.

- - -End Footnotes- - -

It is so ORDERED this 29 day of July 2004.

SARAH EVANS BARKER, JUDGE

United States District Court

Southern District of Indiana

EXHIBIT 3

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1601, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability that published in the *Federal Register*.

For questions on the content of the draft document contact Wallace Adams, 301-594-5618.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Biopharmaceutics
April 2003

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

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April 2003

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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Note: The following stand alone documents will be provided when completed.

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance For Industry[1]

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations to applicants who are planning product quality studies to measure bioavailability (BA) and/or establish bioequivalence (BE) in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for locally acting drugs in nasal aerosols (metered-dose inhalers (MDIs)) and nasal sprays (metered-dose spray pumps). This guidance addresses BA and BE studies of prescription corticosteroids, antihistamines, anticholinergic drug products, and the over-the-counter (OTC) mast-cell stabilizer cromolyn sodium. Applicability of the guidance to other classes of intranasal drugs that may be developed in the future should be discussed with the appropriate CDER review division.

This guidance does not cover studies of nasal sprays included in an applicable OTC monograph[2] or studies of (1) metered-dose products intended to deliver drug systemically via the nasal route or (2) drugs in nasal nonmetered dose atomizer (squeeze) bottles that require premarket approval.

[1] This guidance has been prepared by the Oral Inhalation and Nasal Drug Products Technical Committee, Locally Acting Drug Products Steering Committee, Biopharmaceutics Coordinating Committee, with contributions from the Inhalation Drug Products Working Group, the Chemistry, Manufacturing, and Controls Coordinating Committee, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] 21 CFR 341, Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use.

The first draft of this guidance was issued in June 1999 for comment. Because of changes made as a result of comments received to the docket, internal discussions, and deliberations of the Advisory Committee for Pharmaceutical Science, we have decided to issue the guidance once again in draft. A series of attachments are being developed and will be posted with this draft guidance as stand alone documents on the Internet as soon as they have been completed.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Product quality studies provide information that pertains to the identity, strength, quality, purity, and potency of a drug product. These studies include information on chemistry, manufacturing, and controls (CMC), microbiology, BE and certain aspects of BA. A BE study is normally used to compare a test product (T) to a reference product (R) • the to-be-marketed product is compared to a pivotal clinical trial material, and a generic product is compared to a reference listed drug. A BE study thus provides information on product quality. BA studies for ensuring product quality relate to the release of the active ingredient or active moiety from the drug product (Williams et al., 2000). BA studies may also address biopharmaceutical and clinical pharmacology issues, such as absorption, distribution, and elimination of the active ingredient and its metabolites and dose proportionality. These latter BA/PK studies provide information beyond product quality BA characterization and would also be included in the Human Pharmacokinetics section (Item 6) of an NDA. These latter studies are not the subject of this guidance. Rather, this guidance discusses studies that focus on product performance (i.e., release of a drug substance from a drug product). Subsequent references to BA studies in this guidance *refer only to BA studies for ensuring product quality.*

This guidance should be used with other, more general CMC and BA and BE guidances available from CDER.[3] Product quality information is different from, yet complementary to, the clinical safety and efficacy information that supports approval of an NDA. For information on the type of safety and efficacy studies that may be requested for a new active ingredient/active moiety intended for local action in the nose, or for a new product such as a nasal aerosol that may include an active ingredient/active moiety previously approved in a nasal spray, we recommend appropriate CDER review staff be consulted.

Note: Detailed CMC information relevant to nasal aerosols and nasals sprays is presented in the final guidance *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* • •

[3] Guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

Chemistry, Manufacturing, and Controls Documentation.[4] The document provides complementary information on the BA/BE testing methods recommended in this guidance.

A. BA and BE Data

Bioavailability is defined at 21 CFR 320.1 as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." "*Bioequivalence* is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." "BA and BE are closely related, and the same approach used to measure BA in an NDA can generally be followed in establishing BE for an NDA or ANDA. Although BA may be comparative, establishing BE specifically involves a comparison of the BA of one product with the BA of another product. BE is usually established using (1) a criterion to allow the comparison, based on means and/or variances for BA measures, (2) a confidence interval for the criterion, and (3) a BE limit (goalpost) for the criterion.

BA and BE data must be provided in accordance with the regulations.[5] BA and BE can be established using in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in vitro studies, or, in certain cases, using in vitro studies alone.[6] BA and BE assessments for locally acting nasal aerosols and sprays are complicated because delivery to the sites of action does not occur primarily after systemic absorption. Droplets and/or drug particles are deposited topically. The drug is then absorbed and becomes available at local sites of action. A drug administered nasally and intended for local action has the potential to produce systemic activity, although plasma levels do not in general reflect the amount of drug reaching nasal sites of action. Systemic exposure following nasal administration can occur either from drug absorbed into the systemic circulation from the nasal mucosa, or after ingestion and absorption from the gastrointestinal tract (Daley-Yates et al., 2001). For these reasons, BA and BE studies generally would consider both local delivery and systemic exposure or systemic absorption.

1. Local Delivery BA/BE Concepts

For local delivery, BA is a function of several factors, including release of the drug substance from the drug product and availability to local sites of action. Release of the drug from the drug product produces droplet or drug particle sizes and distribution

[4] A draft guidance, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing, and Controls Documentation*, was issued in October 1998. Once finalized, it will represent the Agency's thinking on this topic.

[5] 21 CFR 320.21, Requirements for submission of in vivo bioavailability and bioequivalence data.

[6] 21 CFR 320.24, Types of evidence to establish bioavailability or bioequivalence.

patterns within the nose that are dependent upon the drug substance, formulation, and device characteristics. Availability to local sites of action is usually a function of droplet or drug particle sizes and distribution patterns, as well as drug dissolution in the case of suspension products, absorption across mucosal barriers to nasal receptors, and rate of removal from the nose. From a product quality perspective, the critical issues are release of drug substance from drug product and delivery to the mucosa. Other factors are of lesser importance.

A critical question in assessing product quality BA and BE is the extent to which one can rely on in vitro methods alone, or upon in vitro methods plus clinical endpoints, to measure (benchmark) BA and/or establish BE. In vitro methods are less variable (Newman et al., 1995; Borgstrom et al., 1996; Suman et al., 2002), easier to control, and more likely to detect differences between products if they exist, but the clinical relevance of these tests, or the magnitude of the differences in the tests, can not always be clearly established. Clinical endpoints may be highly variable (Welch et al., 1991; Meltzer et al., 1998) and relatively insensitive to dose differences over an eightfold or higher dose range (Advisory Committee for Pharmaceutical Science, 2001), thus insensitive in detecting potential differences between products. However, clinical studies can unequivocally establish effectiveness of the drug product.

In this guidance, the recommended approaeh for solution formulations of locally acting nasal drug products, both aerosols and sprays, is to rely on in vitro methods to assess BA. To establish BE, the recommended approach relies on (1) qualitative and quantitative sameness of formulation of test and reference products, (2) comparability in container and closure systems, and (3) in vitro methods that demonstrate equivalent performance. This approach is based on the premise that in vitro studies would be more sensitive indicators of drug delivery to nasal sites of action than would be clinical studies. For solution formulations, see Section IV.B.1.

The recommended approach for establishing BA and BE of suspension formulations of locally acting nasal drug produets, both aerosols and sprays, is to conduct in vivo studies in addition to in vitro studies.[7] As with the solution formulation aerosols and sprays, to establish BE, the approach also relies on qualitative and quantitative sameness of formulation of test and reference products and comparability in container and closure systems. We recommend that in vitro studies be coupled with a clinical study for BA, or a BE study with a clinical endpoint (Section VI), to determine the delivery of drug substance to nasal sites of action. In vivo studies are recommended because of an inability at the present time to adequately characterize drug particle size distribution (PSD) in aerosols and sprays (Sections V.B.3, 4). Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation.

[7] Types of in vivo BE studies that may be submitted in support of an ANDA include, in addition to pharmacokinetic studies, tests in humans in which an acute pharmacological effect is measured as a function of time and appropriately designed comparative clinical trials for demonstration of BE (21 CFR 320.24).

2. Systemic Exposure and Systemic Absorption BA/BE Concepts

Locally acting drugs are intended to produce their effects upon delivery to nasal sites of action without relying on systemic absorption. Although systemic absorption may contribute to clinical efficacy for certain corticosteroids and antihistamines, the consequences of systemic absorption (e.g., hypothalamic-pituitary-adrenal (HPA) axis suppression by corticosteroids) are generally undesirable. In the absence of validated in vitro methodology for characterizing drug PSD for suspension products and when measurable plasma levels can be obtained, this guidance recommends PK studies to measure systemic exposure BA or to establish systemic exposure BE (see Section VII). For suspension products that do not produce sufficient plasma concentrations to allow assessment of systemic exposure, clinical studies or BE studies with a pharmacodynamic or clinical endpoint are recommended to measure systemic absorption BA and establish systemic absorption BE, respectively (Section VIII). For a schematic representation of recommended studies, see Appendix A: Decision Tree.

B. CMC and In Vitro BA Tests (Noncomparative) Versus BE Tests (Comparative)

Generally, CMC tests help characterize the identity, strength, quality, purity, and potency of the drug product and assist in setting specifications (tests, methods, acceptance criteria) to allow batch release. These tests have a different purpose than do BA/BE tests, which focus on the release of the drug substance from the drug product. Some of the in vitro BA/BE tests described in this guidance may be the same as CMC tests for characterization and/or batch release. CMC and in vitro BA tests have acceptance criteria. In vitro BE tests have BE limits. A specification (test, method, acceptance criterion) for a CMC test for batch release or an in vitro BA test is usually based on general or specific manufacturing experience. For example, a CMC test such as dose content uniformity has acceptance criteria based on repeated manufacturing of batches. In contrast, BE tests have limits that are not usually based on manufacturing experience, but are part of equivalence comparisons between test and reference products. BE limits may be based on a priori judgments and may be scaled to the variability of the reference product (see Appendices C, E). When conducted premarket for an NDA, some of the in vitro BA tests described in this guidance can be noncomparative and serve primarily to document (benchmark) the product quality BA of a pioneer product.

III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM

A. Formulation

Particle size, morphic form, and state of solvation of an active ingredient have the potential to affect the BA of a drug product as a result of different solubilities and/or rates of dissolution. We recommend for an ANDA of a suspension formulation, data demonstrating comparable PSD and morphic form of the drug particles, size and number of drug aggregates in the dosage form, and hydrous or solvate form of the active drug in the dosage form to the reference listed drug, be

provided, where possible. Where impossible, the rationale for not providing this full set of comparative data is requested. For suspension formulations marketed in more than one strength, we recommend that the drug substance in each strength product be micronized under identical parameters, and the PSD of the resultant bulk drug used in each product strength be identical.

B. Container and Closure System

Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated accessories, and protective packaging, which together constitute the drug product. Similarly, nasal sprays usually consist of the formulation, container, pump, actuator, protection cap, and protective packaging, which together constitute the drug product.

For nasal aerosols and nasal sprays approved under an ANDA, we recommend BE be documented on the basis of validated in vitro and vivo tests, or, in the case of solutions, validated in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is greatest when the test product uses the same brand and model of devices (particularly the metering valve or pump and the actuator) as used in the reference product. If this is infeasible, we recommend that valve, pump, and actuator designs be as close as possible in all critical dimensions to those of the reference product. We recommend that metering chamber volumes and actuator orifice diameters be the same. For a nasal spray, spray characteristics can be affected by features of the pump design, including the precompression mechanism, actuator design, including specific geometry of the orifice (Kublic and Vidgren 1998), and the design of the swirl chamber. The external dimensions of the test actuator are expected to ensure comparable depth of nasal insertion to the reference actuator. A test product is expected to attain prime within the labeled number of actuations for the reference product. We recommend you consider the volume of components of the device that must be filled to deliver an actuation, including the internal diameter and length of the diptube because this volume can influence the number of actuations required to prime a spray pump.

IV. DOCUMENTATION OF BA AND BE

A. NDAs

For product quality, we recommend that in vitro BA studies be provided in NDAs for solution and suspension products, and in vivo BA studies be provided for suspension products. These data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the in vivo performance of the product. Where the formulation and/or method of manufacture of the pivotal clinical trial product changes in terms of physicochemical characteristics of the drug substance, the excipients, or the device characteristics, BE data using in vitro tests (for solution and suspension products) and in vivo tests (for suspension products) may be useful in certain circumstances to ensure that the to-be-marketed product (T) is comparable to very similar clinical trial batches and/or to batches used for stability testing (R) (Section V.A.1). We recommend sponsors discuss the usefulness of these BE approaches with the appropriate CDER review staff.

247
248 **B. ANDAs**
249
250 For product equivalency, we recommend that the drug concentration in the test and reference
251 product formulations not differ by more than • 5 percent. In addition, we recommend that the
252 inactive ingredients in the test product formulation be qualitatively (Q_1)[8] the same and
253 quantitatively (Q_2) essentially the same as the inactive ingredients in the formulation of the
254 reference listed drug, and the container and closure recommendations of Section III be followed.
255 Quantitatively *essentially the same* has been determined by CDER to mean that the
256 concentration or amount of the inactive ingredient(s) in the test product would not differ by more
257 than • 5 percent of the concentration or amount in the reference listed drug. We recommend a
258 side-by-side Q_1 and Q_2 comparison of the compositions of the test and reference listed drug
259 formulations be provided. Please also provide a side-by-side comparison of the components of
260 the container and closure system, listing brand and model, dimensions of critical components
261 (Section IIIB), and engineering drawings if possible.
262
263 *1. Solution Formulations*
264
265 We believe in vitro tests alone can be relied on to document BE for nasal solution
266 formulation products intended for local action. This approach is based on an
267 understanding that for solution products, equivalent in vitro performance and adherence
268 to Q_1 and Q_2 recommendations and to container and closure recommendations will
269 ensure comparable delivery to the nasal mucosa and to the respiratory and
270 gastrointestinal tracts. Suggested methodology and validation approaches for the
271 recommended tests are provided in Section V. Suggested statistical methods to allow
272 comparisons will be discussed in the appendices to this document. When in vitro data
273 fail to meet acceptance criteria, the applicant is encouraged to modify the test product to
274 attain equivalent in vitro performance. Because of insensitivity to potential differences
275 between T and R, in vivo studies would not be sufficient in the face of failed in vitro
276 studies.
277
278 *2. Suspension Formulations with PK Systemic Exposure Data*
279
280 To document BE for suspension formulation products intended for local action, we
281 recommend both in vitro and in vivo data be used. In vivo studies would include both a
282 BE study with a clinical endpoint (local delivery) and a pharmacokinetic study (systemic
283 exposure). This approach is only applicable for those suspension formulation products
284 that produce sufficiently high plasma concentrations of the moiety(ies) to be measured to
285 allow reliable analytical measurement for an adequate length of time after nasal
286 administration. Suggested methodology and validation approaches for the recommended
287 tests are provided for in vitro studies in Section V, and for in vivo studies in Sections VI
288 and VII. As with solutions, in vivo studies would not be sufficient in the face of failed in
289 vitro studies (i.e., in vitro BE studies that fail to meet the statistical tests) even though the

[8] See 21 CFR 314.94(a)(9)(v).

BE study with a clinical endpoint or the PK study meets the statistical test. Conversely, ANDAs with acceptable in vitro data, but with in vivo data that fail to meet the statistical tests, would be insufficient to establish BE.

3. Suspension Formulations without PK Systemic Exposure Data

For those products intended for local action that produce blood or plasma levels that are too low for adequate measurement, given current assay constraints, a BE study with a clinical endpoint to establish equivalent local delivery to nasal sites (Section VI) and a study with a pharmacodynamic or clinical endpoint to establish equivalent systemic absorption (Section VIII) are recommended. In vivo studies that meet the statistical test would not be sufficient in the face of in vitro studies that fail to document BE. As for suspensions with PK data, ANDAs with acceptable in vitro data, but with in vivo data that fail to meet the statistical tests, would be insufficient to establish BE.

C. Postapproval Change

This document does not cover postapproval changes. Sponsors planning such changes can consult the guidance for industry *Changes to an Approved NDA or ANDA* and contact the appropriate review division prior to instituting the change.

V. IN VITRO STUDIES

A. Batches and Drug Product Sample Collection

1. NDAs

We recommend in vitro BA studies for nasal aerosols and sprays be performed on samples from three or more batches: a pivotal clinical trial batch to provide linkage of in vitro performance to in vivo data; a primary stability batch; and if feasible, a production-scale batch. This selection of batches will ensure consistency of in vitro performance among the three types of batches. If a production-scale batch is unavailable, a second pivotal clinical trial batch or second primary stability batch can be substituted. When three batches are studied, we recommend the batches be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. We prefer that the three batches be studied at the same time, if possible, to remove interstudy variation from the estimation of between batch means and variances.

The BA batches to be studied would be equivalent to the to-be-marketed product and representative of production scale. The manufacturing process for these batches would simulate that of large-scale production batches for marketing (additional information on large-scale batches is provided in the International Conference on Harmonisation (ICH)

guidance for industry Q1A *Stability Testing of New Drug Substances and Products*, Section II.B.3). Complete batch records, including batch numbers of device components used in the batches, would accompany the BA submission.

In vitro BA studies are intended to characterize the means and variances of measures of interest for canisters (nasal aerosols) or bottles (nasal sprays) within a batch and between batches, where applicable. However, under 21 CFR 320.1 and 320.21, the studies can be noncomparative to other formulations or products. The in vitro tests and metrics are described in Section V.B of this guidance. The recommended number of canisters or bottles of each batch to be used in the above studies, and recommendations for statistical analyses, are described in Appendix B.

2. ANDAs

In vitro BE studies for nasal aerosols and sprays would generally be performed on samples from each of three or more batches of the test product and three or more batches of the reference listed drug. Test product samples would be from the primary stability batches used to establish the expiration dating period. When three batches are studied, we recommend the test product be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. For nasal sprays formulated as solutions, in vitro BE tests can alternatively be performed on three sublots of product prepared from one batch of the solution.[9]

The BE batches to be studied would be equivalent to the to-be-marketed product. The manufacturing process of these batches would simulate that of large-scale production batches for marketing. Complete batch records, including batch numbers of device components used in the batches or sublots (for solution nasal sprays) would accompany the BE submission.

Reference product samples would be from three different batches available in the marketplace. The recommended in vitro tests and metrics are described in Section V.B. The recommended number of canisters or bottles of each product and batch to be used in the above studies, and recommended statistical approaches, are described in Appendices C, D and E.

B. Tests and Metrics

In vitro BA and BE for locally acting drugs delivered by nasal aerosol or nasal spray are usually characterized using seven tests:

[9] For solution formulation nasal sprays, variability in in vitro BE study data between batches is expected to be due primarily to variability in the device components of the product rather than in the solution. Therefore, a single batch of solution can be split-filled into three equal size sublots of product. The sublots would be prepared from three different batches of the same device (pump and actuator) components.

1. Single Actuation Content Through Container Life
2. Droplet Size Distribution by Laser Diffraction
3. Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor
4. Drug Particle Size Distribution by Microscopy
5. Spray Pattern
6. Plume Geometry
7. Priming and Repriming

These tests are relevant to all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, with the exception of drug particle size distribution by microscopy, which applies only to suspension products. The in vitro tests are summarized in Table 1.

We recommend you validate all in vitro tests for accuracy and precision prior to the study. For applicable studies, instrument settings established during prestudy validation would be used in the study. For comparative studies, use of the same settings will ensure that T and R are studied under the same instrumental conditions. The in vitro tests would be conducted on canisters or bottles selected in a random manner from the test batch, including units from the beginning, middle, and end of the production run. Actuation should be conducted in a manner that removes potential operator bias, either by employing automatic actuation, or by employing blinded procedures when manual actuation is used. However, we recommend automated actuation systems for all comparative in vitro BE tests. These systems are expected to decrease variability in drug delivery due to operator factors, thereby increasing the sensitivity for detecting potential differences between products in the above tests.[10] In addition, it is important that the analyst performing the postactuation evaluations of the collected data be blinded to the identity of the samples. We recommend analytical methods used for analysis of samples from the in vitro tests be validated.[11] Unexpected results and deviations from protocol or SOPs, with justification for deviations, would be reported. Examples include, but are not limited to, canisters or bottles replaced during in vitro analyses, failure to use the specific actuations required by the protocol, and experiments rejected due to assignable causes (e.g., instrument failure, sample collection, or processing errors). The original and reanalyzed data, with the reason for reanalysis, would be tabulated in the study report. The validation reports for the in vitro tests and analytical methods, the randomization procedure, and all test methods or SOPs for each test would accompany the data in the submission. When appropriate, we recommend the test method or SOP include a standardized shaking procedure prior to testing, following labeled instructions, if any.

[10] Automatic actuation systems can be stand-alone or accessories for spray characterization instruments. Systems can include settings for force, velocity, acceleration, length of stroke, and other relevant parameters. Selection of appropriate settings would be relevant to proper usage of the product by the trained patient, and for nasal sprays, may be available from pump suppliers for tests such as Droplet Size Distribution by Laser Diffraction and Spray Pattern. In the absence of recommendations from the pump supplier, we recommend that settings should be documented based on exploratory studies in which the relevant parameters are varied to simulate in vitro performance upon hand actuation. Selected settings used for the in vitro studies would be specified in the test method or SOP for each test for which the system is employed.

[11] A draft guidance for industry entitled *Analytical Procedures and Methods Validation* was issued in August 2000.

In addition to submission of all raw data, the agency would like to see supporting documentation for the following tests: Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry. Documentation includes instrument output reports and photographic or graphic material as applicable. We recommend that documents be clearly labeled to indicate the product (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as appropriate. For Droplet Size Distribution by Laser Diffraction, profiles of droplet size and obscuration or percent transmission over the complete life of the single sprays would be submitted. For Spray Pattern and Plume Geometry, we recommend each image display the relevant BA/BE measures described in this guidance. Supporting documentation for Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry would include representative copies, preferably electronic, of • 20 percent of the total observations. For Spray Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic images rather than paper copies of • 20 percent of the total observations would be submitted, as electronic files are definitive. For automated image analysis of Spray Pattern and Plume Geometry, in addition to the electronic images, we recommend paper copies of a few screen images be submitted as reference samples.

1. Single Actuation Content (SAC) Through Container Life

For noncomparative data, SAC through container life testing is used to characterize the delivery of drug discharged from the actuator of an aerosol or nasal spray relative to label claim through container life. For comparisons of T and R products, this test ensures that the T product delivers an equivalent amount of drug relative to the R product over the labeled number of actuations. The tests are distinct from and do not apply dose content uniformity (DCU) or spray content uniformity (SCU) acceptance criteria.

The dosage unit sampling apparatus for collection of an emitted dose from an aerosol is described in *U.S. Pharmacopeia* (USP) *25*, <601>. We recommend a suitable apparatus be used for collecting an emitted dose from a nasal spray. For both solution and suspension formulations of nasal aerosols and nasal sprays, the mass of drug per actuation would be based on a stability-indicating chemical assay unless use of a nonstability-indicating method is justified. Because the data at beginning (B) lifestage will also be used for confirmation of priming (Section V.B.7), SAC through container life would be based on ***single actuation data per determination***. For BA and BE submissions, the tests would determine delivered (emitted or ex-actuator) drug mass from primed units at the beginning of unit life, at the middle of unit life, and at the end of unit life[12] for nasal aerosols, and at beginning and end of unit life for nasal sprays. The delivered mass of drug substance would be expressed both as the actual amount and as a percentage of label claim. We recommend that mean and variability in SAC through

[12] Based on the labeled number of actuations, this guidance uses the terms *beginning lifestage (B), middle lifestage (M),* and *end lifestage (E)* interchangeably with the terms *beginning of unit life* (the first actuation(s) following the labeled number of priming actuations); *middle of unit life* (the actuation(s) corresponding to 50 percent of the labeled number of actuations); and *end of unit life* (the actuation(s) corresponding to the label claim number of actuations).

container life be determined based on within and between unit (container) data and between batch (or sublot) data. For BE data, equivalence of T and R data would be based on the statistical methodology of Appendix C.

To use the SAC through container life data for priming studies, we recommend acrosols and sprays be unprimed prior to the conduct of the tests. Therefore, for aerosols, the test would be performed at such time that the product meets two conditions: (1) after the lagering period and (2) not less than one month after the last actuation conducted as part of batch release testing. During the time period between batch release and SAC through container life testing, the aerosol product would not be actuated. Also, during this one month period, both T and R acrosols would be stored in the valve upright position, unless labeling indicates that the product be stored in the valve down position, in which case the test would be conducted on products stored in the valve down position. For sprays, the SAC through container life test would be conducted not less than one month after completion of batch release testing. During the time period between batch release and SAC testing, the product would not be actuated.

2. Droplet Size Distribution by Laser Diffraction

Droplet size distribution is an important property influencing the nasal deposition of aerosols and sprays, and we recommend that it be thoroughly characterized.

a. Nasal sprays

We recommend that droplet size distribution be determined using laser diffraction or an appropriately validated alternate methodology.

Laser diffraction is a nonaerodynamic optical method of droplet sizing that measures the geometric size of droplets in flight. Modern laser diffraction instrumentation can provide plots of obscuration (optical concentration) or percent transmission (%T) and droplet size distribution (D_{10}, D_{50}, D_{90}) over the entire life of a single spray. Span ((D_{90} - D_{10})/D_{50}) can be computed from these data. These profile data indicate that each plume can be characterized by three phases: formation, fully developed, and dissipation. For nasal sprays, the general profile for obscuration or percent T versus time can be characterized by a rapid increase in obscuration, or decrease in percent T, early in the life of the spray (formation phase), followed by attainment of a plateau (fully developed phase), then a rapid decrease in obscuration, or increase in percent T, late in the life of the spray (dissipation phase). Changes in droplet size occur coincident with the changes in obscuration or percent T, with droplet sizes attaining plateau values within the same approximate time period as the plateau in obscuration or percent T. Profiles of the droplet size and obscuration or percent T over the complete life of the single sprays are recommended to be determined at each of two distances (see below) to establish the fully developed phase during which data would be collected. Droplet size distribution and span during the fully developed phase are

requested. The sponsor's protocol or SOP would state the criterion selecting the region of the plateau at which droplet size data will be determined (e.g., the average of all scans over the entire plateau, the data of a single scan (sweep) only at the maximum obscuration (or minimum percent T), or the average of a specified range of scans around this obscuration or percent T). This criterion would be established prior to the study for each of the two distances and implemented consistently during the study.

We would also like to see instrument setup and operation conditions. We recommend the instrument be operated within the manufacturer's recommended obscuration or percent T range, which would be stated in the submission, to avoid or minimize multiple scattering (due to high droplet concentration). Avoidance of multiple scattering is preferred to use of a correction algorithm that compensates for this effect.

Single spray droplet size distribution and span would be reported based on volume (mass) rather than count (number of droplets). We would like to request data be provided for nasal sprays at:

- Fully developed phase only
- B and E lifestages
- Two distances from the actuator orifice. For increased ability to detect potential differences between products, it is recommended that the studies be performed within a range of 2 to 7 cm from the orifice, with the two distances separated by 3 cm or more.

b. Nasal acrosols

Droplet size distribution can be determined using laser diffraction or appropriately validated alternate methodology.

We would like to see instrument setup and operation conditions. We recommend the instrument be operated within the manufacturer's recommended obscuration or percent T range, which would be stated in the submission, to avoid or minimize multiple scattering (due to high droplet concentration). Avoidance of multiple scattering is preferred to use of a correction algorithm that compensates for this effect.

Beam steering resulting from refractive index effects due to evaporation of propellant is an additional concern for nasal aerosols. Droplet size distribution would be characterized at distances from the actuator that eliminate or minimize beam steering, if possible. If a correction algorithm is used, we recommend an explanation of the corrections be provided.

We ask that single-spray droplet size distribution and span be reported based on volume (mass) rather than count (number of droplets). Data would be provided for nasal aerosols at:

- Fully developed phase only
- B and E lifestages
- Two distances from the actuator orifice

For both nasal sprays and nasal aerosols, mean D_{10}, D_{50}, D_{90} values for a given bottle or canister can be computed from the mean of up to three consecutive sprays from that unit at each lifestage. However, to assess precision, the data of each spray would also be reported.

3. *Drug in Small Particles/Droplets, or Particle/Droplet Size Distribution by Cascade Impactor*

Sizing of droplets or particles by multistage cascade impactor (CI) measures aerodynamic diameter based on inertial impaction, an important factor in the deposition of drug in the nasal passages. Analytical data should be based on a validated chemical assay.[11] We recommend that analytical runs include at least three or more concentrations of quality control samples that represent the entire range of the standard curve or the expected concentration range of samples from the various stages of the CI. An analytical validation report would accompany the CI data report. The SOP or validation report would indicate the minimum quantifiable mass of drug deposited on each location reported.

a. Nasal sprays: Drug in Small Particles/Droplets

For nasal sprays, the majority of the emitted dose is deposited prior to or on the first stage of the CI test. Small droplets, for this test and dosage form defined as smaller in size than the nominal effective cutoff diameter (ECD) of the top stage of a suitable CI, may potentially be delivered to regions of the airways beyond the nose. This test is intended to determine the amount of drug in small particles/droplets. For example, for USP 25 Apparatus 1 (<601>), an eight stage CI operated with the standard 28.3 liter per minute configuration, small droplets are those under 9.0 microns. For BA, the CI test is intended to quantify the mass of drug in small droplets. For BE, the mass of drug in small droplets for the T product would be less than or equivalent to the corresponding mass of drug from the R product. The comparative test addresses a potential safety concern — an excess of small droplets due to T relative to R might deliver to regions beyond the nose excipients with possible adverse pulmonary effects. The CI test for nasal sprays is not intended to provide PSD of drug or aerosolized droplets.

Measurable levels of drug below the top stage of the CI would be a function of the specific drug product and the experimental setup and procedure, including the

number of actuations and assay sensitivity. Thus, we recommend a validated, highly sensitive assay be used. In Agency experience, a two-liter or larger induction port (expansion chamber) is preferred to a one-liter chamber. We prefer studies use the fewest number of actuations (generally not exceeding 10) justified by the sensitivity of the assay, to be more reflective of individual doses. Drug deposition would be reported in mass units. Mass balance accountability would be reported. Mass balance would be based on drug deposition on each of valvestem, actuator, adapters, induction port, any other accessories, the top stage, and all lower stages to the filter. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis. The total mass of drug below the top stage is of primary interest. Therefore the pooled mass of drug deposited on all lower stages and filter can be reported.

For BA and BE, CI test would be data requested only at the beginning lifestage. Statistical approaches will be provided in Appendices B and D, respectively.

b. Nasal aerosols: Particle/Droplet Size Distribution

CI studies for nasal aerosols would use an induction port (expansion chamber) that maximizes drug deposition below the top stage of the CI. For this reason, a one-liter induction port is preferred to the USP 25 (<601>) induction port, although other sizes may also be appropriate. Agency experience indicates that with a suitable induction port and CI, the amount of drug deposited below the top stage from nasal aerosols formulated with either chlorofluorocarbon or hydrofluoroalkane propellants is of the same order of magnitude as from orally inhaled aerosols. Therefore, unlike for nasal sprays in which the total mass of drug below the top stage is of interest, we recommend a particle/droplet size distribution be provided for this dosage form. Selection of the most suitable CI may be influenced by the effective cutoff diameters (ECDs) of stages of various brands of cascade impactors, the geometry of the induction port, and other factors. The number of actuations recommended for the CI study of aerosols is described in the draft guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products • Chemistry, Manufacturing, and Controls Documentation.* Drug deposition would be reported in mass units. Mass balance accountability would be reported.

For BA and BE, CI data would be requested only at the beginning lifestage. At this time, it is recommended that studies of nasal aerosols use USP 25 Apparatus 1 (<601>) operated at the standard 28.3 liter per minute configuration. We recommend determination of a profile based on drug deposition at 11 sites: (1) sum of valve stem plus actuator; (2) induction port; (3 - 10) eight individual stages; and (11) filter. Deposition in the valve stem plus actuator would be included to provide a profile of drug deposition ex-valve rather than ex-actuator. It should be noted that the in vitro BE limit for the profile comparison depends on

the number of stages and other accessory deposition sites. Statistical approaches for BA and BE will be provided in Appendices B and E, respectively.

4. Drug Particle Size Distribution by Microscopy

For suspension products, drug particle size may be important for rate of dissolution and availability to sites of action within the nose. Therefore, drug particle size distribution (PSD) and extent of agglomerates would be characterized in the spray or aerosol formulation prior to actuation, and in the spray following actuation. Determination of PSD and agglomerates in both the formulation and following actuation are intended to characterize the potential influence of the device on deagglomeration. Determination in the spray is only requested at the beginning lifestage. Nasal spray formulations frequently contain suspended drug substance in the presence of insoluble suspending agent, which complicates the particle size characterization. When examining formulations containing suspending agents, and currently available technology cannot be acceptably validated to determine drug particle size, a qualitative and semi-quantitative method for examination of drug and aggregated drug particle size distribution can be used. We recommend studies of nasal sprays include placebo product to provide an estimate of the occurrence of apparent drug particles (*false positives*) due to excipient. Evaluation may use light microscopy or other appropriate means.

For NDAs and ANDAs of both sprays and aerosols, we recommend drug PSD and agglomerates data be provided in the BA or BE submission, along with a description of the test method. Sponsors can submit representative photomicrographs, if desired. For BE, PSD by light microscopy, even if qualitative or semi-quantitative, can be useful to the applicant to estimate particle size relative to the precursor product prior to further product development and testing. These data are supportive, and formal statistical testing is not applicable.

5. Spray Pattern

Spray pattern studies characterize the spray either during the spray prior to impaction, or following impaction on an appropriate target such as a thin-layer chromatography (TLC) plate. Spray patterns for certain nasal spray products may be *spoked* or otherwise irregular in shape.

Spray patterns can be characterized and quantitated by either manual or automated image analysis, if validated. Both analyses will allow shape and size to be determined. Automated analysis systems may also allow determination of center of mass (COM; unweighted for image intensity) and/or center of gravity (COG; weighted for image intensity) within the pattern to be determined. COG is of greater interest and is preferred in the automated analyses of spray patterns. Automated image analysis is expected to increase objectivity in spray pattern measurement. The technology enables the perimeter of the true shape of the spray pattern to be determined, identifies COM and/or COG, and enables the area within the perimeter to be quantitated, thus its use is encouraged.

Equivalence of spray patterns between T and R products can be established based on a combination of qualitative and quantitative measures:

- Comparative visual inspection for shape. For the automated analyses, the true shapes identified by the software serve as the basis of comparison (qualitative). Establishment of qualitative sameness of T and R spray pattern shapes is a prerequisite to the quantitative analyses in the following two bullets.
- Equivalent area within the perimeter of the true shape for automated analysis, or equivalent D_{max} for manual analysis (quantitative)
- Equivalent ovality (ellipticity) ratio (quantitative)

a. For nonimpaction systems

Spray patterns can be visualized using a system based on a laser light sheet and high-speed digital camera that enables visualization of a pattern perpendicular to the axis of the nasal spray. The perimeter of the true shape, area within the perimeter (to include a high proportion, e.g., • 95% of the total pattern), COG, and D_{max} (longest diameter) and D_{min} (shortest diameter) that pass through the COG and extend to the perimeter of the true shape, can be determined based on automated analysis using time-averaged images over the duration of a single spray. Software settings can be established during prestudy validation and the settings should be used consistently in the study. Statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio (D_{max} divided by D_{min}).

b. For impaction systems

The number of sprays per spray pattern would preferably be one. We recommend that the visualization technique be specific for the drug substance. If exploratory studies document that a drug-specific reagent cannot be found, a nonspecific visualization reagent can be used. We recommend that application of the reagent be controlled to maintain the details of the image intensity of the pattern.

Manual analysis

The approximate COM would be identified, and D_{max} and D_{min} drawn through this center. The two lines may not be orthogonal to each other. Representative plots can be submitted, and each figure can be marked with the COM, D_{max} and D_{min}, each based on visual analysis. The ovality ratio would be provided for each spray pattern. Statistical analysis at each distance would be based on equivalence of D_{max} and ovality ratio.

Automated analysis

The automated image analysis software can define the perimeter of the true shape of the spray pattern to include a high proportion (e.g, • 95%) of the total pattern. T and R would both be sprayed on each TLC plate to ensure measurement of the spray pattern at the same intensity range for a given plate. D_{max} and D_{min} would pass through the COM or the COG, as appropriate, and extend to the perimeter of the true shape. Statistical analysis at each distance would be based on equivalence of area within the perimeter and ovality ratio.

c. For both nonimpaction and impaction systems

The information above would apply to spray patterns in which the COM or COG falls within the perimeter of the image of the actual spray pattern, and the D_{max} axis doesn't extend outside of the perimeter. Infrequently, the COM or COG may fall outside the perimeter of the spray pattern, and/or the D_{max} axis may cross the perimeter. Horseshoe-shaped and certain other patterns may cause such an effect. When this occurs, automated analysis using a system that has the capability of fitting the perimeter with an appropriate geometric shape is recommended. Statistical analysis at each distance would be based on equivalence of area within the perimeter of the ***true shape*** of the spray pattern (not within the fitted geometric shape), and ovality ratio, where D_{max} and D_{min} are computed from the ***fitted geometric shape*** (e.g., ellipse).

For all cases above, we recommend spray patterns be determined based on:

- Single actuations (nonimpaction systems), or preferably single actuations (impaction systems)
- Beginning lifestage only
- Two distances from the actuator orifice, which allow discriminatory capability between individual pump units and between T and R products. For nasal sprays, these distances are recommended to be at least 3 cm apart within the range of 3 to 7 cm.

For manual quantitation of spray patterns based on impaction studies such as TLC plate methodology, we recommend the submission include copies, preferably electronic, of images of representative spray patterns at two distances, and each figure would clearly indicate the estimated COM (manual analysis), D_{max} and D_{min}. When automated image analysis software is used for impaction studies, data would be presented in electronic files. For automated image analysis of either impaction or nonimpaction studies, electronic files would be definitive. Submission of electronic files is recommended to avoid printer-dependent variations in spatial calibration of images. These files would contain the images, showing the COG or COM and the perimeter of the true shape of the spray pattern, and the accompanying quantitation reports. Each image would also include a legible scale used for measurement.

Some automated image analysis software may not include automated quantitation of spray pattern images. For such cases, the analyst would determine and display the quantitative parameters on the electronic image. As mentioned above, quantitation of electronic images would be definitive.

6. *Plume geometry*

Plume geometry describes a side view of the aerosol cloud parallel to the axis of the plume, and we recommend it be based on high-speed photography, a laser light sheet and high speed digital camera, or other suitable methods. The image would be *snapshot*, not time-averaged. Quantitation can be by manual analysis or automated image analysis.

During the very early life of an aqueous nasal spray plume, formulation may exit the actuator orifice as a narrow stream that subsequently forms a relatively stable, fully developed, conical plume prior to separating from the orifice. We recommend plume angle, width, and height, all quantitated by the same analytical method, be reported at a single delay time while the fully developed phase of the plume is still in contact with the actuator tip. The applicant would provide documentation that the plume is fully developed at the selected delay time. The angle would be based on the conical region of the plume extending from a vertex that occurs at or near the actuator tip. Plume angle based on spray pattern dimensions and distance from actuator tip to an impaction surface is not appropriate. For this guidance, the recommended plume width would be the width at a distance equal to the greater of the two distances selected for characterization of the spray pattern. Plume width data would thus complementary to spray pattern data obtained at the same distance. Plume height would be the distance from the actuator orifice (sprays) or end of the inhaler tube (aerosols) to the leading edge of the plume. We request that the criteria for defining the plume angle, width, and height borders be provided.

Plume geometry would be performed at:

- Beginning lifestage only
- One side view only
- A single delay time

The submission would include photographs when quantitation is by manual analysis, or digital images when quantitation is by automated image analysis. Each image would also include a legible scale used for measurement, and the delay time would be clearly indicated. Images would clearly indicate the plume angle, width, and height. When automated image analysis is used, quantitation of electronic images would be definitive. Manual quantitation based on paper copies of electronic images would not be appropriate.

We recommend plume geometry measurements be summarized as mean, geometric mean, and %CV. Comparative data would be supportive, thus for BE studies, the ratio of

the geometric mean of the three batches of T to that of the three batches of R, based on log transformed data, would fall within 90 – 111% (point estimates) for plume angle and width. Due to subjectivity in the measurement of plume height, point estimates would not be applicable.

7. Priming and Repriming

Priming and repriming data will ensure delivery of the labeled dose of drug following labeled instructions for use. Priming would be established based on the same B lifestage data obtained for the single actuation content (SAC) through container life study (Section V.B.1). For products approved under an NDA, priming and repriming data based on single actuations would be provided in the CMC portion of the submission.

For products approved under an ANDA, the labeling would be the same as that for the R product, except for specific changes described in the regulations (21 CFR 314.94(a)(8)(iv)). For nasal sprays and some nasal aerosols, the R product labeling (package insert and/or patient package insert) describes the number of actuations to prime the product on initial use and on repriming following one or more periods of nonuse (e.g., 24 hours and 7 days following last dose). For these products, we request priming and repriming data for T and R products. Studies would follow the recommended time periods described in Section V.B.1 between lagering and/or batch release testing and conduct of the priming test. Priming and/or Repriming studies would not be requested when the R product lacks priming and/or repriming instructions, respectively.

We recommend that priming and repriming data for T in multiple orientations be provided in the CMC portion of the ANDA submission. Therefore, for the BE submission, studies can be based on products stored in the valve upright position, with the exception of nasal aerosols in which R labeling recommends storage in the valve down position. For the latter products, priming data, and repriming data when applicable, would be provided following storage in the valve down position. Priming studies would be based on the emitted dose of the single actuation at B lifestage immediately following the specified number of priming actuations in the R product labeling. For ANDAs, priming would be established providing that the geometric mean emitted dose of the 30 canisters or bottles calculated from the SAC data at B lifestage falls within 95 – 105 percent of label claim. Repriming would be similarly established based on a single actuation following the specified number of repriming actuations in the R product labeling. Although noncomparative to R, the priming studies would be essential to the BE submission to document that each product delivers the labeled dose within the number of actuations stated in the R product labeling, thus ensuring that the SAC through container life studies are conducted on primed T and R products.

VI. CLINICAL STUDIES FOR LOCAL DELIVERY

A. General Information

1. NDAs

At the present time, of the classes of drugs covered in this guidance, only certain corticosteroids are formulated as suspension formulation nasal aerosols and nasal sprays and require in vivo studies as a component of the BE or BA submission (21 CFR 320.21). The same adequate and well-controlled clinical trials in humans conducted under an authorized IND, used to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR 320.24).

2. ANDAs

Clinical studies are at times incapable of showing a dose-response relationship and may not be consistently reproducible. However, a showing of dose-response is not necessary for BE studies with a clinical endpoint, as these studies are intended only to confirm the lack of important clinical differences between T and R suspension formulation nasal aerosol and nasal spray products (Advisory Committee for Pharmaceutical Science, 2001). For an ANDA, an authorized Bio-IND will be needed for the conduct of a BE study with a clinical endpoint.[13]

A determination of bioequivalence of a rhinitis BE study with a clinical endpoint for locally acting nasal suspension drug products would be based on the following premises for T relative to R products:

- Qualitative and quantitative sameness of formulation
- Comparability in container and closure systems
- Equivalence of in vitro tests
- Equivalence of systemic exposure or systemic absorption
- Equivalence of the local delivery study.

A number of FDA guidances provide information about the general conduct of clinical studies, including clinical studies to document BA and BE: *General Considerations for Clinical Trials* (International Conference on Harmonisation (ICH) E8); *Structure and Content of Clinical Study Reports* (ICH E3); *Good Clinical Practice: Consolidated Guidance* (ICH E6); *Statistical Principles for Clinical Trials* (ICH E9), and *Choice of Control Group and Related Issues in Clinical Trials* (ICH E10).

B. Clinical Study Batches

[13] Office of Generic Drugs Policy and Procedure Guide # 36-92, *Submission of an "Investigational New Drug Application" to the Office of Generic Drugs (OGD)*, October 13, 1992.

We recommend that the batch used for the BA study be the same pivotal clinical trial batch used in the in vitro BA studies (Section V.A). Where BE studies are conducted for an NDA, the batches of test and reference products would be the same batches employed in the in vitro testing. Each of the T and R batches used to establish local delivery BE for an ANDA would be one of the three batches used for the in vitro BE studies. We recommend that the inactive ingredients of the placebo (P) product meet Q_1 and Q_2 recommendations relative to the R product (Section IV.B); the P container and closure would meet the recommendations of Section III.B.

C. Clinical BE Study Design and Subject Inclusion Criteria

The study design would be the traditional treatment study in which T and R are assessed for a two-week duration. The two-week duration, in addition to allowing a comparison of equivalent efficacy, will also allow for an assessment of safety and tolerability over a reasonable period of use. We recommend the study be conducted at the lowest labeled adult recommended dose in an attempt to optimize study sensitivity. Primed products according to labeling instructions prior to dosing. Ensure that priming occurs out of range of the patients, to avoid inhalation of drug fired to waste. Documentation would rely on the inclusion of a test product placebo (P) dosed at the same frequency and number of actuations per nostril as T and R.

A study population consisting of seasonal allergic rhinitis (SAR) patients will allow documentation of BE, which may extend to all indications in product labeling for locally acting nasal corticosteroids. In addition to a history of SAR, we recommend patients have a positive test for relevant specific allergens (e.g., allergen skin test) and be experiencing a defined minimum level of symptom severity at the time of study enrollment. We discourage the inclusion of patients with other significant diseases including asthma, with the exception of mild intermittent asthma.

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study of 14 days duration, preceded by a 7-day placebo run-in period to establish a baseline and to identify placebo responders.[14] We recommend placebo responders be excluded from the study to increase the ability to show a significant difference between active and placebo treatments (efficacy analysis), and to increase sensitivity to detect potential differences between T and R products (equivalence analysis). The protocol would define *placebo responders* a priori. Whether the drug is labeled for once or twice daily dosing, clinical evaluations would be made twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo run-in period and the 14-day randomized treatment period. Scoring should be made immediately prior to each dose, to reflect the previous 12 hours (*reflective* scores) and how the patient is feeling at the time of evaluation (*instantaneous* or *snapshot* scores). Because the primary BE endpoint would be based on reflective symptom scores, placebo responders should be identified based on reflective scores, although BE endpoints would include both reflective and instantaneous scores.

[14] A draft guidance for industry entitled *Allergic Rhinitis: Clinical Development Programs for Drug Products* was issued in April 2000. This guidance discusses general protocol issues including blinding. Once finalized, it will represent the Agency's thinking on this topic.

We recommend baseline scoring preferably consist of reflective AM and PM scoring on Days 5, 6, and 7 of the placebo run-in period, and AM scoring (prior to drug dosing) on Day 1 of the 14 day randomized treatment period, resulting in 7 total AM and PM ratings. Placebo responders would be identified based on the mean total nasal symptom score (TNSS) over the 7 total AM and PM ratings. The study protocol would state the minimum qualifying reflective TNSS for enrollment at screening, and the same minimum qualifying TNSS would be met based on the mean of the 7 total AM and PM ratings prior to each patient's participation in the randomized portion of the study. We recommend randomization occur after evaluation of the 7 total AM and PM ratings, and the randomized portion of the study can start in the morning of Day 1 after the AM baseline scoring.

Symptom scores during the randomized treatment period would consist of the PM score on Day 1, and the 26 AM and PM ratings on Days 2 to 14, resulting in 27 total ratings. We recommend the study be multicenter to avoid potential investigator bias. A double dummy design is not recommended for study blinding of aqueous nasal sprays due to a concern that the doubled fluid volume may result in washing the drug from its nasal deposition sites, potentially resulting in an altered safety and efficacy profile. However, study blinding is a critical consideration, and we recommend a description of how the T, R and P products are to be masked be carefully described in the study protocol.

We recommend the ***equivalence analysis*** be conducted as an evaluable (per protocol) analysis rather than an intent-to-treat analysis. The evaluable population would consist of compliant patients who missed no more than a specified number of days of symptom scores, took no contraindicated concurrent medications, and had no protocol violations. The protocol would describe the specific criteria used to exclude randomized subjects, resulting in the reduced subset of subjects for analysis (*FDA Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*, Section III.B.9). In addition to the equivalence analysis, an ***efficacy analysis*** would be conducted to demonstrate study sensitivity to the T and R products. The efficacy analysis would be conducted as an intent-to-treat analysis, and the intent-to-treat population would be clearly defined. Because specific study recommendations are not provided in this guidance, we recommend a protocol for a BE study with a clinical endpoint for a specific suspension drug product be submitted prior to the conduct of the study to the appropriate review division at FDA.

D. Clinical BE Study Endpoints

The endpoints for the ***equivalence*** and ***efficacy analyses*** should be patient self-rated *TNSS*. These most often include a composite score of runny nose, sneezing, nasal itching, and congestion, although addition of non-nasal symptoms to the composite score maybe pertinent for certain drug products.[15] TNSS is a categorical variable, classified into a number of discrete categories, as opposed to a continuous variable. A common allergic rhinitis rating system uses a

[15] Draft guidance *Allergic Rhinitis: Clinical Development Programs for Drug Products*, was issued in April 2000, once finalized it will represent the Agency's thinking on this topic.

four-point scale with signs and symptoms ordered in severity from 0 (no symptoms) to 3 (severe symptoms), as follows[16]:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

We recommend the endpoints for the equivalence and efficacy analyses be expressed as mean change from baseline (pretreatment) of the TNSS, expressed in absolute units, rather than percent change from baseline. The study report would include the daily AM and PM 12-hour reflective symptom scores. In addition, the report would include the mean symptom score over the 7 total AM and PM ratings of the placebo run-in period and the mean symptom score over the 27 ratings of the randomized treatment period. For the equivalence and efficacy analyses, the ***primary*** endpoint would be reflective scores for the 12-hour pooled TNSS over the two-week randomized portion of the study. However, instantaneous scores would also be provided as a ***secondary*** endpoint. Statistical approaches for analysis of the rhinitis study data are provided in Appendix F.

Safety assessments would be made before (at screening or baseline) and at end-of-treatment. Adverse events would be reported daily.

VII. PK STUDIES FOR SYSTEMIC EXPOSURE

A. General Information

The Agency recommends that plasma concentration-time profiles from BA and BE studies be used to evaluate systemic exposure for suspension drug products that produce sufficiently high concentrations of the moiety(ies) to be measured to allow reliable analytical measurement for an adequate length of time after nasal administration. The recommended moiety(ies) to be measured in the BA and BE studies are described elsewhere.[17]

Systemic drug levels that occur with locally acting drug products are generally in the low ng/mL or low pg/mL range, depending on the drug and the drug product. Validated bioanalytical methodology may be available for many of the nasal corticosteroid drugs. For these drugs, pilot studies are not needed prior to conducting the full-scale PK study. If validated methodology is unavailable, a small-scale, single-dose pilot study, or when appropriate, a small-scale, multiple-

[16] Other scoring systems were proposed in the draft guidance *Allergic Rhinitis: Clinical Development Programs for Drug Products* April 2000. Once finalized, it will represent the Agency's thinking on this topic.

[17] *Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations* (October 2000). Once finalized it will represent the Agency's thinking on this topic.

dose pilot study, may be helpful in assessing the proposed analytical methodology and determining whether sufficiently high drug concentrations are attained. A PK study for systemic exposure would be preferred to a PD or clinical study for systemic absorption (Section VIII). If a sponsor has convincing data based on unsuccessful attempts to conduct the PK study in order for a PD or clinical study for systemic absorption could be used. If systemic exposure were established based on a PK study, a PD or clinical study for systemic absorption (Section VIII) would not be requested.

B. Study Batches

The Agency recommends that the BA batch used for the PK systemic exposure study be a pivotal clinical trial batch. Alternatively, a PK batch similar to the batch used in a pivotal clinical trial can be used, in which case we recommend that any differences between the PK batch and the pivotal clinical trial batch be discussed with the appropriate CDER review division prior to the study. If the PK batch is not one of the three batches used for the in vitro BA studies (Section V.A.1), make sure that in vitro BA data are provided for the PK batch using the same protocols as for the three batches.

For a BE study, the batches of T and R would be the same batches used for the clinical study for local delivery, and each of these batches would be one of the three batches used for the in vitro BE studies.

C. Study Design and Subject Inclusion Criteria

The BA study to characterize systemic exposure can be one of the same PK studies conducted to address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA study can be conducted in healthy subjects or allergic rhinitis (AR) patients. Where appropriate, the BA study would include a reference product that may be an oral or intravenous solution, oral suspension, or other nasal product. Consultation with the appropriate review division is recommended regarding whether a comparative or noncomparative BA study is appropriate.

For an NDA or an ANDA, the in vivo BE study would be conducted with a replicate or nonreplicate randomized crossover design. For aqueous nasal sprays, the study would be conducted at the maximum labeled adult dose to maximize plasma drug levels, while avoiding the possibility of alteration of the drug deposition pattern within the nose at higher volumes when dosed above label claim. The deposition pattern could be altered due to loss of drug from the nasal cavity at these higher volumes, due either to drainage into the nasopharynx or externally from the nasal cavity. Although alteration of the deposition pattern may be less likely for a nasal aerosol when dosed above the maximum labeled number of actuations, the same study design and dose as for aqueous nasal sprays would be followed. We recommend that subjects for the study be healthy, with exclusions primarily for reasons of safety. The study protocol would include information regarding time interval between doses to each nostril and subject head position during dosing.

This guidance recommends that the PK study generally be conducted as a single-dose study. Such studies are more sensitive than multiple dose studies in assessing rate of release of the drug substance from the drug product into the systemic circulation. In addition, the nasally dosed corticosteroids tend to have biologic half-lives ranging from less than one hour up to about eight hours. For these products, when dosed either once or twice daily, systemic accumulation is expected to be relatively low, thus a multiple dose study may not result in a more reliable analytical measurement. However, there may be drugs that, due to pharmacokinetic characteristics, yield higher concentrations in a multiple-dose study, enabling the drug moiety(ies) of interest to be measured more reliably than in a single-dose study. For these drugs, a multiple-dose PK study would be preferred to a single-dose study.

D. Study Measures

The following BA and BE measures are considered pivotal[17] in a single-dose study: $AUC_{0-tlast}$ (a measure of total exposure); $AUC_{0-\infty}$ (a measure of total exposure); and C_{max} (peak exposure). If $AUC_{0-\infty}$ cannot be determined reliably due to inability to estimate k_{el} accurately, total exposure would be based only on $AUC_{0-tlast}$. The following BA and BE measurements and plasma concentrations provide supportive PK characterization: plasma concentrations at each sampling time; T_{max}; and k_{el}. The following BA and BE measurements are considered pivotal for a multiple-dose study: $AUC_{0-\tau}$ (total exposure), where τ is the dosing interval; and C_{max} (peak exposure). T_{max} data should also be provided as supportive characterization.

Statistical analysis information is provided in Appendix G.

VIII. PD OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION

A. General Information

As stated in Section VI.A, at present only certain corticosteroids are formulated as suspension products and require product quality in vivo studies. For those suspension drug products for which the moiety(ies) to be measured in the blood or plasma (Section VII) are too low to allow reliable analytical measurement for an adequate length of time, PD or clinical endpoint studies serve as measures of systemic absorption (Section II.A.2). However, ***PK studies as measures of systemic exposure are preferred if at all possible.*** As stated in Section VII, if a sponsor has convincing data based on unsuccessful attempts to conduct the PK study a PD or clinical study would be used in lieu of the PK study. The BA study to characterize systemic absorption may be one of the same clinical studies conducted to establish the safety of the drug product. The study would be conducted under an authorized IND in support of a forthcoming NDA (21 CFR 314.126).

If a PD or clinical study is to be conducted (see previous paragraph), the recommended systemic absorption BE study design for nasal corticosteroids would be assessment of the HPA axis. The study would be conducted at the maximum labeled adult dose of the nasal aerosol or nasal spray to maximize study sensitivity. However, the study design would be based on an understanding

that the maximum labeled dose over a 6-week period (Section VIII.C) may not result in detectable adrenal suppression by T and R because this dose may be at or near the bottom of the adrenal suppression dose-response curve. In addition to a test product placebo (P), we recommend an active control such as prednisone be included to ensure that the study is sufficiently sensitive to detect a drug effect (sensitivity analysis). Ensure that the active control dose is sufficiently large and the duration sufficiently long to produce a statistically significant response relative to placebo, with a duration sufficiently short to minimize undue exposure or risk to subjects. Determination of the optimum active control dose and dosing regimen may call for a pilot study by the sponsor. The pilot study may determine that an initial phase of the 6-week study period may use a matching active control placebo, with active control given over the remainder of the study period, in an effort to reduce patient exposure to the active control. The pilot study can also provide an estimate of the number of subjects to be included in the pivotal study to yield a statistically significant difference in the HPA axis endpoint between the active control and the test product placebo (i.e., the aerosol or spray placebo). It may also allow estimation of the number of subjects to be included to characterize any HPA axis effects or lack thereof and to allow conclusions about any relative effects of T versus P and R versus P ("relative assessment of the HPA axis"; Appendix G.B). Conduct of the study in allergic rhinitis (AR) patients will allow an efficacy assessment to evaluate compliance with the study protocol (efficacy analysis). Therefore, AR patients, rather than healthy, non-allergic patients are recommended as the study population. We also recommend that other measures of compliance be instituted, including before and after weighing of the aerosol or spray container and diary entry of drug use.

Because this section does not provide specific recommendations, we recommend sponsors submit prior to the conduct of the study a protocol for a BE study with a PD or clinical endpoint for a specific drug product to the appropriate review division at FDA. For an NDA, the same adequate and well-controlled clinical trials in humans conducted under an authorized IND, used to establish the safety and effectiveness of a drug product in support of a forthcoming NDA (21 CFR 314.126), can be used in some cases to establish BA or, when comparative, BE (21 CFR 320.24). For an ANDA, if the maximum single or total daily dose of the active control in the pilot or full-scale study exceeds that specified in the labeling of the selected active control drug product, an authorized Bio-IND will be needed.[13]

B. Clinical Study Batches

The Agency recommends the BA batch used for the study be a pivotal clinical trial batch used in the in vitro BA studies (Section V.A). For BE studies for an NDA, the batches of T and R would be batches used in in vitro testing. For an ANDA, the batches of T and R used for the systemic absorption study would be the same batches used for the clinical study for local delivery. Each of these batches would be one of the three batches used for the in vitro BE studies. Formulation and device recommendations for the P are described in Section VI.B. An active control such as prednisone is recommended. For blinding, matching active control placebo (identical in appearance to the active control) is also recommended.

C. Clinical BE Study Designs and Subject Inclusion Criteria

We recommend the study be conducted as a placebo and active-controlled, randomized, double-blind, parallel design comparing T and R for a 6-week duration. The study would not be conducted as a subset of the 2-week local delivery rhinitis study (Section VI). Subjects would be patients with a history of AR. The *relative assessment of HPA axis suppression* would be conducted as an evaluable (per protocol) analysis. The sensitivity analysis and efficacy analysis would he conducted as intent-to-treat analyses. The protocol would specify whether placebo responders will or will not be excluded from the analysis. We recommend that subjects be domiciled within the clinical study center during the days of HPA axis assessment. Domiciling the subjects during the 24-hour urine or plasma collection periods can help to conduct the study-related procedures reliably and completely. T and R would be dosed at the maximum labeled adult dose. P would be dosed at the same frequency and number of actuations per nostril as T and R. As stated above, the study would include an active control such as prednisone. Four study arms would be included: T, R, P, and the active control. The randomized portion of the study would be conducted according to a double-blinding design (i.e., all subjects would receive both the active control (either the active control itself or a matching placebo of the active control) and a spray or aerosol (either active or placebo)). The four treatment groups would be T plus matching active control placebo, R plus matching active control placebo, P plus matching active control placebo, and P plus active control. The matching active control placebo would be dosed on days when the active control is not taken, including the placebo run-in period. We recommend the number of centers conducting the HPA assessment be kept to a minimum to avoid center-to-center variability. A double-dummy design is not recommended for aqueous nasal sprays, as explained in Section VI.C. However, study blinding is a critical consideration, and we recommend a description of how the T, R and P products are to be masked be carefully described in the study protocol.[18]

The expected effect for the active control would be far larger than that for the T and R products. The sample size of the active control arm group may therefore be smaller in size than for the other study arms. We recommend the sample size for the T and R study arms be sufficient to characterize any HPA axis effects or lack thereof to allow conclusions about any relative effects of T versus P and R versus P, as stated in Section VIII.A.

We recommend timed urine or plasma samples for determination of 24-hour urinary free cortisol (UFC) or 24-hour plasma cortisol levels, respectively, be collected. Collections would be made prior to dosing (baseline) and during the last 24 hours of the 42 days of dosing (i.e., over the day 41 – 42 period) while the drug is being actively dosed.

D. Clinical BE Study Endpoints for Corticosteroids

Whether the drug is labeled for once or twice daily dosing, the endpoint can be either 24-hour urinary free cortisol (UFC), based on a full 24-hour urine collection, or plasma cortisol levels

[18] A draft guidance entitled *Allergic Rhinitis: Clinical Development Programs for Drug Products* was issued in April 2000. Once finalized, this guidance will represent the agency's thinking on this topic.

collected every 4 hours over a 24-hour period, with exclusion of the middle of the night sample. For the UFC endpoint, urinary creatinine would also be measured to confirm completeness of the 24-hour collection. The UFC value would not be corrected for creatinine. We recommend for the plasma cortisol endpoint, both AUC(0-24) and the trough (maximum effect) concentration during the dosing interval should be determined. The sensitivity analysis endpoint would be baseline-adjusted prior to analysis. Raw data would be provided for the relative assessment of HPA axis suppression. Efficacy analysis TNSS data would be expressed as change from baseline.

Statistical approaches for each of the analyses are provided in Appendix G.B.

IX. NUMBER OF RESERVE SAMPLES FOR BA AND BE TESTING

Reserve samples must be retained for BA and BE studies (21 CFR 320.38 and 320.63) conducted in vivo or in vitro. The regulations state that each reserve sample must consist of a sufficient quantity of samples to permit FDA to perform five times all of the release tests required in the application or supplemental application. Dose content uniformity or spray content uniformity release tests alone usually require 30 units (canisters or bottles) per batch. Performance of other release tests requires additional units. The number of reserve sample units required for three batches of T and R could exceed 1000 units (up to 250 units for each batch of T and R) based on the *five-times-quantity* requirement.

The Agency has determined that in lieu of the *five-times-quantity* requirement, the quantity of inhalant (nasal aerosol or nasal spray) test article (T) and reference standard (R) retained for testing and analyses be at least 50 units for each batch.[19] For NDAs, three batches are needed for BA studies. Thus, we recommend at least 50 units from each of the three batches of nasal spray or nasal aerosol be retained. However, where the reference product is another nasal aerosol or nasal spray, at least 50 units of that batch would also be retained. For ANDAs, at least 50 units of each of three batches would be retained for each of T and R used in in vivo or in vitro BE studies. For NDAs and ANDAs, if the in vivo or in vitro studies include placebo aerosols or sprays, at least 50 units of each placebo batch would also be retained. These recommendations apply only to nasal aerosols and nasal sprays for local action covered in this guidance and which are marketed as multiple dose products, typically labeled to deliver 30 or more actuations per canister or bottle. The number of reserves for nasal aerosols and nasal sprays delivering less than 30 actuations per canister or bottle is not addressed in this guidance. Additional information regarding retention of BA and BE testing samples is pending.[20]

[19] Quantity of Reserve Samples, Preamble to final rule, Retention of Bioavailability and Bioequivalence Testing Samples, 58 FR 25918-26, 1993, IIC21.

[20] A draft guidance for industry entitled *Handling and Retention of BA and BE Testing Samples* was issued in August 2002. Once finalized, it will represent the Agency's thinking on this topic.

X. MULTIPLE STRENGTHS

A small number of nasal sprays for local action are available in two strengths. Current examples are (1) ipratropium bromide nasal spray, a solution formulation, and (2) beclomethasone dipropionate nasal spray, a suspension formulation. Lower strengths of a product ordinarily would achieve the lower dose per actuation using a lower concentration formulation, without changing the actuator and metering valve or pump (other than diptube due to different volumes of product or other factors) used in the higher strength product. The following sections describe recommended BA and BE studies for low strengths of nasal sprays for which BA or BE for the higher strengths has previously been established. Recommendations are also provided for cases in which BA or BE is initially established on the low-strength product. No approved nasal aerosols are available in multiple strengths, thus BA and BE recommendations are not considered for these products.

A. Solution Formulation Nasal Sprays

We recommend the BA of lower or higher strength solution formulation nasal sprays be based on conduct of all applicable in vitro tests described in Section V. These studies are generally noncomparative in character. Documentation of BE between T and R products would follow the recommendations described in Section III regarding formulation and container and closure system. Abbreviated in vitro testing, as follows, is recommended to document BE of the low-strength T product to the low-strength R product, provided BE of the high-strength product has been documented.

In vitro test	High Strength	Low Strength
Single Actuation Content Through Container Life	B, E[a]	B, E
Priming and Repriming	Yes	Yes
Droplet Size Distribution by Laser Diffraction	B, E	B
Drug in Small Particles/Droplets by Cascade Impactor	B	No
Spray Pattern	B	B
Plume Geometry	B	No

[a] Beginning (B), Middle (M), End (E)

With the exception of the reduced testing, the Agency recommends the same protocols and acceptance criteria used to establish BE of the high-strength products be used for the low strength products. In vivo studies are not needed for documentation of BA or BE of solution formulation nasal sprays. Initial documentation of BE of the low-strength product would be based on all applicable in vitro tests described in Section V. For subsequent documentation of BE for the high-strength product, all applicable in vitro tests described above for the high-strength product would be conducted.

B. Suspension Formulation Nasal Sprays

We recommend BA of lower strength suspension formulation nasal sprays be based on conduct of all applicable in vitro tests described in Section V and systemic exposure studies, assuming availability of bioanalytical methodology to allow measurement of systemic concentrations. In the absence of this methodology, we suggest BA for systemic absorption be documented through pharmacodynamic or clinical studies.

BE conditions for the lower strength product would include:

1. Documentation of BE for the high-strength test and reference products, based on acceptable comparative formulations and container and closure systems, comparative in vitro data, and comparative in vivo data

2. Acceptable comparative formulations and container and closure systems for the low-strength test and reference products

3. Acceptable comparative studies for low-strength test and reference products for all applicable in vitro tests in Section V

4. Proportionally similar Single Actuation Content Through Container Life between high- and low-dose test product and high- and low-dose reference product

In vivo studies would not be needed for documentation of BE of the lower strength products.

For cases in which an ANDA applicant initially documents BE on the low-strength suspension formulation product, and subsequently submits an ANDA for the high-strength product, full in vitro and in vivo documentation of BE would be provided for the high-strength product.

XI. SMALLER CONTAINER SIZES

Nasal aerosols and nasal sprays may be available in two container sizes. Current examples are: (1) beclomethasone dipropionate nasal aerosol, a suspension formulation; (2) fluticasone propionate nasal spray, a suspension formulation; and (3) cromolyn sodium nasal spray, a solution formulation. Smaller container sizes of nasal aerosols would be formulated with the same components and composition, metering valve, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Smaller container sizes of nasal sprays would be formulated with the same components and composition, pump, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Where this is the case, no further documentation of either BA or BE is necessary. However, re-establishing proper priming, given a change in the volume of components of the device that will be filled to deliver an actuation, may in some cases be appropriate (Section V.B.7).

1324
1325
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TABLE 1
RECOMMENDED IN VITRO STUDIES FOR BA AND BE OF NASAL AEROSOLS AND NASAL SPRAYS

TEST[1]	BA AND BE STUDY MEASURE(S)	BE MEASURE(S) FOR STATISTICAL EVALUATION	LIFESTAGE(S) B (beginning), M (middle), E (end)	STATISTICAL EVALUATION FOR BE PBE (population bioequivalence)	GUIDANCE SECTIONS
Single Actuation Content Through Container Life	Drug mass per single actuation	Same as previous column	B, M, E (aerosols) B, E (sprays)	PBE	V.B.1, App. B, C
Droplet Size Distribution by Laser Diffraction	D_{10}, D_{50}, D_{90}, span at 2 distances	D_{50}, span	B, E	PBE	V.B.2, App. B, C
Drug in Small Particles/Droplets by Cascade Impactor	Drug mass below upper stage	Same as previous column	B (sprays)	PBE modified to be one-sided with respect to the mean comparison	V.B.3, App. B, D
Particle/Droplet Size Distribution by Cascade Impactor	Drug mass on individual accessories, stages, etc – profile analysis	Deposition profile	B (aerosols)	Profile analysis	V.B.3, App. B, E
Drug Particle Size Distribution by Microscopy for suspensions	Drug CMD; extent of agglomerates	Same as previous column	B	Not applicable	V.B.4
Spray Pattern	Automated analysis: area, ovality ratio at 2 distances or Manual analysis: D_{max}, ovality ratio at 2 distances	Qualitative – shape comparison Quantitative - Same as previous column	B	PBE for area and ovality ratio (automated analysis) or D_{max} and ovality ratio manual analysis	V.B.5, App. C
Plume Geometry	Height, width, and cone angle of one side view at one delay time	Width and cone angle of one side view at one delay time	B	Point estimates	V.B.6
Priming and Repriming	Drug mass per single actuation at first primed or reprimed actuation	Same as previous column for Priming, and Repriming if in precursor product (R) labeling	B (Priming) Lifestage not specified (Repriming)	Point estimate relative to label claim if in precursor product (R) labeling	V.B.7

[1] Although alternate test methods may be appropriate for certain tests, if validated, we recommend sponsors planning to use such methods contact the appropriate reviewing division prior to use.

EXHIBIT 4

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Wallace P. Adams (301) 594-5651 (CDER).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 1999

Guidance for Industry

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

Additional copies are available from:

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Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 1999

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May 27, 1999

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

I. INTRODUCTION

This guidance is intended to provide recommendations to applicants who are planning product quality studies to measure bioavailability (BA) and/or establish (BE) in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for locally acting drugs in nasal aerosols (metered-dose inhalers (MDIs)) and nasal sprays (metered-dose spray pumps). Product quality includes chemistry, manufacturing, and controls (CMC), microbiology, certain BA information, and BE information (i.e., information that pertains to the identity, strength, quality, purity, and potency of a drug product). Product quality BA and BE are reflective of potency, in that release of the drug substance from the drug product should be assessed and controlled to achieve a reproducibly potent product. BA studies can address many questions, but this guidance discusses studies that focus on product performance (i.e., release of drug substance from drug product). A BE study is normally used to compare a test product (T) to a precursor product (R) — the to-be-marketed product is compared to a pivotal clinical trial material; a generic product is compared to a reference listed drug .

Product quality approaches should be similar for all nasal aerosols and nasal sprays where the active ingredient/active moiety is intended for local action, regardless of drug or drug class. This guidance should be used with other, more general CMC and BA and BE guidances available from CDER (Internet, http://www.fda.gov/cder/guidance/index.htm). Product quality information is different from, yet complementary to, the clinical safety and efficacy information that supports approval of an NDA. For information about the type of safety and efficacy information that may be needed for a new active ingredient/active moiety intended for local action in the nose, or for a new product such as a nasal aerosol that may include an active ingredient/active moiety previously approved in a nasal spray, appropriate CDER review staff should be consulted.

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[1] This guidance has been prepared by the Oral Inhalation and Nasal Drug Products Technical Committee, Locally Acting Drug Products Steering Committee, Biopharmaceutics Coordinating Committee, with contributions from the Inhalation Drug Products Working Group, the Chemistry, Manufacturing, and Controls Coordinating Committee, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on product quality information related to inhalation aerosols and metered dose spray pumps for nasal delivery. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance covers BA and BE studies of prescription corticosteroids, antihistamines, anticholinergic drug products, and the over-the-counter (OTC) mast-cell stabilizer cromolyn sodium. The guidance does not cover studies of nasal sprays included in an applicable OTC monograph or studies of (1) metered-dose products intended to deliver drug systemically via the nasal route[2] or (2) drugs in nasal nonmetered dose atomizer (squeeze) bottles that require premarket approval.

Note: Detailed chemistry, manufacturing, and controls information relevant to nasal aerosols and nasals sprays are presented in two draft guidances, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler(DPI) Drug Products — Chemistry, Manufacturing, and Controls Documentation* (October 1998) and *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Product* (available June 1999). These draft guidances, when finalized, will provide complementary information on the BA/BE testing methods recommended in this guidance.

II. BACKGROUND

A. BIOAVAILABILITY AND BIOEQUIVALENCE DATA

Bioavailability is defined at 21 CFR 320.1 as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action." *Bioequivalence* is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." BA and BE are closely related, and the same approach to measure BA in an NDA should generally be followed in establishing BE for an NDA or ANDA. Although BA may be comparative, establishing BE specifically involves a comparison of the BA of one product with the BA of another product. BE is usually established using (1) criteria based on means and/or variances for BA measures, (2) BE intervals (goalposts), which are standards to allow a determination of equivalence when confidence intervals are computed using the specified criteria, and (3) confidence intervals for the criteria.

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[2] 21 CFR 341. Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use.

BA and BE data should be provided in accordance with the regulations.[3] BA and BE may be established by in vivo (pharmacokinetic (PK), pharmacodynamic (PD), or clinical) and in vitro studies, or, with suitable justification, by in vitro studies alone.[4] BA and BE assessments for locally acting nasal aerosols and sprays are complicated because delivery to the sites of action does not occur primarily after systemic absorption. Droplets and/or drug particles are deposited topically, then absorbed and becomes available at local sites of action. Systemic exposure following nasal administration can occur either from drug absorbed into the systemic circulation from the nasal mucosa, or after ingestion and absorption from the gastrointestinal tract. A drug administered nasally and intended for local action is therefore likely to produce systemic activity, although plasma levels of the drug do not reflect the amount of the drug reaching nasal sites of action. For these reasons, BA and BE studies should consider both local delivery and systemic exposure or systemic absorption.

1. Local Delivery BA/BE Concepts

For local delivery, BA is determined by several factors, including release of drug substance from the drug product and availability to local sites of action. Release of drug from the drug product is characterized by distribution patterns and droplet or drug particle size within the nose that are dependent upon drug substance, formulation, and device characteristics. Availability to local sites of action is a function of the above release factors, as well as drug dissolution in the case of suspension products, absorption across mucosal barriers to nasal receptors, and rate of removal from the nose. From a product quality perspective, the critical issues are release of drug substance from drug product and delivery to the mucosa. Other factors are of lesser importance. A critical question in assessing product quality BA and BE is the extent to which one can rely on in vitro methods alone, or upon in vitro methods plus clinical endpoints, to measure (benchmark) BA and/or establish BE. In vitro methods are less variable, easier to control, and more likely to detect differences between products if they exist, but the clinical relevance of these tests, or the magnitude of the differences in the tests, is not always clearly established. Clinical endpoints may be highly variable and relatively insensitive in detecting differences between products, but can unequivocally establish effectiveness.

In this guidance, the recommended approach for solution formulations of locally acting nasal drug products is to rely on in vitro methods to assess BA and BE. This approach is based on the assumption that in vitro studies would be more sensitive indicators of drug delivery to nasal sites of action than would be clinical studies. Drug particle size

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[3] 21 CFR 320.21, Requirements for submission of in vivo bioavailability and bioequivalence data.

[4] 21 CFR 320.24, Types of evidence to establish bioavailability or bioequivalence.

distribution (PSD) in suspension formulations has the potential to influence the rate and extent of availability to nasal sites of action and to the systemic circulation. For suspension formulation products, however, due to the inability to adequately characterize drug PSD (see section V.B.2), in vivo studies should be conducted as part of the studies establishing product quality BA and BE. In vitro studies should be coupled with a clinical study for BA, or a BE study with a clinical endpoint for BE, to determine the delivery of drug substance to local nasal sites of action. An in vivo systemic exposure or systemic absorption study should also be conducted for suspensions (see section II.A.2). For solution formulations, see section IV.B.1.

2. Systemic Exposure and Systemic Absorption BA/BE Concepts

Locally acting drugs are intended to produce their effects upon delivery to nasal sites of action without relying upon systemic absorption. Although systemic absorption may contribute to clinical efficacy for certain corticosteroids and antihistamines, the consequences of systemic absorption (e.g., HPA suppression by corticosteroids) are generally undesirable. In the absence of validated in vitro methodology for characterization of drug PSD for suspension products, and when measurable plasma levels can be obtained, this guidance recommends PK studies to measure systemic exposure BA or establish systemic exposure BE (section VII). For suspension products that do not produce sufficient concentrations to assess systemic exposure, clinical studies or BE studies with a clinical endpoint should be used to measure systemic absorption BA and establish systemic absorption BE, respectively (section VIII). For a schematic representation of recommended studies, see the Decision Tree for In Vivo Product Quality BA and BE Studies for Nasal Aerosols and Nasal Sprays (p. 35).

BA recommendations in this guidance are limited to *product quality* BA. For investigational new drugs (INDs) and NDAs, not only should product quality BA be provided, but BA/PK studies should also be included in the Human Pharmacokinetics section (Item 6) of the NDA for nasal aerosols and nasal sprays for local action, whether formulated as solutions or suspensions, and whether or not validated methods of determining drug PSD are available. These PK data provide biopharmaceutic and clinical pharmacology information beyond product quality BA characterization.

B. CMC TESTS AND IN VITRO BA TESTS (NONCOMPARATIVE) VERSUS BE TESTS (COMPARATIVE)

Generally CMC tests help characterize the identity, strength, quality, purity, and potency of the drug product and assist in setting specifications (tests, methods, acceptance criteria) to allow batch release. These tests have a different purpose than do BA/BE tests, which focus on release

of drug substance from drug product. Some of the in vitro BA/BE tests described in this guidance for nasal aerosols and sprays may be the same as CMC tests for characterization and/or batch release. A specification (test, method, acceptance criterion) for a CMC test for batch release is usually based on general or specific manufacturing experience. For example, a CMC test such as dose content uniformity has acceptance criteria based on repeated manufacturing of batches. Bioequivalence limits for BE studies are not usually based on manufacturing experience, but are part of equivalence comparisons between test and reference products. Equivalence comparisons normally include (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit for the criterion. BE limits may be based on a priori judgments and may be scaled to variability of the reference product (see Section IX). When conducted premarket for an NDA, some of the in vitro BA tests described in this guidance can be noncomparative and serve primarily to document (benchmark) the product quality BA of a pioneer product.

III. FORMULATION AND CONTAINER AND CLOSURE SYSTEM

A. FORMULATION

Particle size, morphic form, and state of solvation of the active ingredient have the potential to affect the BA of the drug product as a result of different solubilities and/or rates of dissolution. For an ANDA of a suspension formulation, the PSD of the active drug in the dosage form should be the same as that of the reference listed drug, as discussed in Section V.B. Comparative information on the morphic form of the drug particles, and size and number of drug aggregates in the dosage form, should be provided. In addition, documentation of the same anhydrous or solvate form should be provided. For suspension formulations marketed in more than one strength, the drug substance in each strength product should be micronized under identical parameters, and the PSD of the resultant bulk drug should be identical in each strength product.

B. CONTAINER AND CLOSURE SYSTEM

Nasal aerosols consist of the formulation, container, valve, actuator, dust cap, associated accessories (e.g., spacers), and protective packaging, which together constitute the drug product. Similarly, nasal sprays consist of the formulation, container, pump, actuator, protection cap, and protective packaging, which together constitute the drug product.

For nasal aerosols and nasal sprays approved under an ANDA, BE should be documented on the basis of validated in vivo and vitro tests, or, in some cases, validated in vitro tests alone may be appropriate. Assurance of equivalence on the basis of in vitro tests is greatest when the test product uses the same brand and model of devices (particularly the metering valve or pump and the actuator) as used in the reference product. If this is not feasible, valve, pump, and actuator

designs should be as close as possible in all critical dimensions to those of the reference product. Metering chamber volumes should be the same. For nasal aerosols, overall actuator design (Byron 1990), including actuator orifice diameter, should be the same. For a nasal spray, spray characteristics may be affected by features of the pump design, including the precompression mechanism, actuator design, including specific geometry of the orifice (Kublic and Vidgren 1998), and design of the swirl chamber. The external dimensions of the test actuator should ensure comparable depth of nasal insertion to the reference actuator. A test product should attain prime within the labeled number of actuations for the reference product. Consideration should be given to the *dead volume* of the device, including the internal diameter and length of the diptube, because this volume can influence the number of actuations required to prime a spray pump.

IV. DOCUMENTATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

A. INDs/NDAs

For INDs/NDAs, in vitro BA studies for solutions and suspensions, and in vivo studies for suspensions, should be provided. These data are useful as a benchmark to characterize the in vitro performance, and for suspensions, the in vivo performance of the product based on the clinical efficacy and either systemic exposure for a PK study, or systemic absorption for a clinical safety study. Where the formulation and/or method of manufacture of the pivotal clinical trial product changes in terms of physicochemical characteristics of the drug substance, the excipients, or the device characteristics, BE data using in vitro tests (for solutions and suspensions) and in vivo tests (for suspensions) may be useful in certain circumstances during the preapproval period to ensure that the to-be-marketed product (T) is comparable to very similar clinical trial batches and/or to batches used for stability testing (R) (section V.A.1). Sponsors should discuss the usefulness of these BE approaches with appropriate CDER review staff.

B. ANDAs

1. Solution Formulations

In vivo studies, such as seasonal allergic rhinitis (SAR) studies to establish equivalent delivery to nasal sites, or HPA suppression studies for corticosteroids to establish equivalent systemic absorption, are not considered necessary for nasally administered solution drug products intended for local action. Thus, reliance on in vitro tests alone to document BE is suitable for nasal solution formulation products intended for local action. This approach is based on an understanding that for solution products, equivalent in vitro performance, inactive ingredients that are qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and adherence to container and closure recommendations of section III will ensure comparable

delivery to the nasal mucosa and to the gastrointestinal tract. Quantitatively *essentially the same* has been determined by CDER to mean that the concentration or amount of the inactive ingredient(s) in the test product should not differ by more than ±5 percent of the concentration or amount in the reference listed drug. Suggested methodology and validation approaches for the recommended tests are provided in section V. Suggested methods to allow comparisons using a criterion, BE limits, and a confidence interval approach are discussed in section IX. When in vitro data fail to meet acceptance criteria, the applicant is encouraged to modify the test product to attain equivalent in vitro performance. Because of insensitivity to potential differences between T and R, in vivo studies will not be sufficient in the face of in vitro studies that fail to document BE.

2. Suspension Formulations with PK Systemic Exposure Data

To document BE for suspension nasal formulation products intended for local action, both in vitro and in vivo data should be used. Inactive ingredients also should be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and the container and closure recommendations of section III should be followed. In vivo studies should include both a pharmacokinetic study (systemic exposure) and a BE study with a clinical endpoint (local delivery). This approach is only applicable for those suspension formulation products that produce sufficiently high drug concentrations in blood or plasma after nasal administration to obtain meaningful AUC and C_{max} data. Methodology and validation approaches for the recommended tests are provided for the in vitro studies in section V, and for the in vivo studies in sections VI and VII. As with solutions, in vivo studies will not be sufficient in the face of in vitro studies that fail to establish BE (i.e., in vitro BE studies that fail to meet the statistical test discussed in section IX result in a failed BE study) even though the BE study with a clinical endpoint or the PK study meets the statistical test.

3. Suspension Formulations without PK Systemic Exposure Data

For suspension nasal formulation products, inactive ingredients should be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the reference listed drug, and the container and closure recommendations of section III should be followed. In addition, for those products intended for local action that produce blood or plasma levels that are too low for adequate measurement, given current assay constraints, a BE study with a clinical endpoint to establish equivalent local delivery to nasal sites (section VI) and a study with a pharmacodynamic or clinical endpoint to establish equivalent systemic absorption (section VIII) are recommended. In vivo studies that meet the statistical test will not be sufficient in the face of in vitro studies that fail to document BE.

C. POSTAPPROVAL CHANGE

For an NDA submitted under 505(b)(1) of the Food, Drug, and Cosmetic Act, the primary need for BE documentation would be between the reference product before and the reference product after very limited changes. For an ANDA and for an NDA submitted in accordance with section 505(b)(2) of the Food, Drug, and Cosmetic Act, the primary documentation of BE for the changed product is the reference or pioneer product. At this time, no guidance is available as to when BE should be redocumented in the presence of any postapproval changes, either for an NDA or ANDA. Sponsors planning such changes should contact the appropriate review division prior to instituting the change.

V. BIOAVAILABILITY AND BIOEQUIVALENCE: IN VITRO STUDIES

A. BATCHES AND DRUG PRODUCT SAMPLE COLLECTION

1. INDs/NDAs

In vitro product quality BA studies for nasal aerosols and sprays should generally be performed on samples from three batches. The batches should include a pivotal clinical trial batch, a primary stability batch, and if feasible, a production scale batch, to provide linkage of in vitro performance to in vivo data. If a production scale batch is not available, a second pivotal clinical trial batch can be substituted.

The above BA batches should be equivalent to the to-be-marketed product. The manufacturing process of these batches should simulate that of large-scale production batches for marketing (additional information on large-scale batches is provided in the International Conference on Harmonisation (ICH) guidance for industry Q1A *Stability Testing of New Drug Substances and Products* (September 1994), section V.B). Complete batch records, including batch numbers of device components used in the batches, should accompany the BA submission.

In vitro BA studies are intended to characterize the means and variances of measures of interest for canisters (nasal aerosols) or bottles (nasal sprays) within a batch and between batches, where applicable. However, under 21 CFR 320.1 and 320.21, the studies may be noncomparative to other formulations or products. The in vitro tests and metrics are described in section V.B. The test method or standard operating procedure (SOP) for each test should accompany the data in the submission. The recommended number of canisters or bottles of each batch to be used in the above studies, and recommendations for statistical analyses, are described in section IX.

2. ANDAs

In vitro BE studies for nasal aerosols and sprays should generally be performed on samples from each of three batches of the test product and three batches of the reference listed drug. Test product samples should be from the primary stability batches used to establish the expiration dating period. Test product should preferably be manufactured from three different batches of the drug substance, different batches of critical excipients, and container and closure components. For nasal sprays formulated as solutions, in vitro BE tests can alternatively be performed on three sublots of product prepared from one batch of the solution.[5]

The above BE batches should be equivalent to the to-be-marketed product. The manufacturing process of these batches should simulate that of large-scale production batches for marketing (ICH Q1A *Stability Testing of New Drug Substances and Products* (September 1994), section V.B). Complete batch records, including batch numbers of device components used in the batches or sublots (for solution nasal sprays) should accompany the BE submission.

Reference product samples should be from three different batches available in the marketplace. The recommended in vitro tests and metrics are described in section V.B. The recommended number of canisters or bottles of each product and batch to be used in the above studies, and recommended statistical approaches, including suggested boundaries for each of the studies, are described in section IX.

B. TESTS AND METRICS

In vitro BA and BE for locally acting drugs delivered by nasal aerosol or nasal spray are characterized by six tests:

1. Dose or Spray Content Uniformity Through Container Life
2. Droplet and Drug Particle Size Distribution
3. Spray Pattern
4. Plume Geometry
5. Priming and Repriming
6. Tail Off Profile

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[5] For solution formulation nasal sprays, variability in in vitro BE study data between batches is expected to be due primarily to variability in the device components of the product rather than in the solution. Therefore, a single batch of solution may be split-filled into three equal size sublots of product. The sublots should be prepared from three different batches of the same device (pump and actuator) components.

The in vitro test information described below is summarized in Table 1 (p. 35).

All in vitro tests should be conducted on test canisters or bottles selected in a randomized manner from the test batch, including units from the beginning, middle and end of the production run. BE tests should be conducted in a blinded manner, or should use another approach that removes potential analyst bias, without interfering with product performance. Automated actuation stations are recommended for all comparative in vitro BE tests to decrease variability in drug delivery due to operator factors (including removal of potential analyst bias in actuation) and increase the sensitivity for detecting potential differences between products in any of the above tests.[6] The blinding procedure should also be extended to postactuation evaluations. The randomization procedure and the test method or SOP for each test should accompany the data in the submission.

1. Dose or Spray Content Uniformity Through Container Life

Sampling apparatus for collection of dosage units from aerosols is described in *U.S. Pharmacopeia 23/National Formulary 18* (Tenth Suppl, 15 May 1998). A suitable apparatus should be used for collection of dosage units from nasal sprays. For both solution and suspension formulations of nasal aerosols and nasal sprays, the mass of drug delivered per single (unit) dose should be determined based on a stability-indicating chemical assay. A single dose represents the minimum number of sprays per nostril specified in the product labeling. For a nasal product for which the minimum single usual dose is one actuation in each nostril, the single dose should be based on one actuation. For a nasal product for which the minimum usual dose is two actuations in each nostril, the single dose should not exceed two actuations. For BA and BE studies, dose or spray content uniformity data should be determined on primed units at the beginning of unit life, at the middle of unit life, and at the end of unit life[7] for nasal aerosols, and at beginning and end of unit life for nasal sprays. Mean dose or spray content uniformity and variability

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[6] Automated actuation stations may be stand-alone systems or accessories for laser diffraction instruments. Stations may include settings for actuation force, actuation velocity, hold time, return time, delay time between actuations, length of stroke, and number of actuations. Selection of appropriate settings should be relevant to proper usage of the nasal aerosol or nasal spray by the trained patient, and should be documented based on exploratory studies in which actuation force, actuation time, and other relevant parameters are varied. These studies should accompany the validation data. Selected settings used for the comparative in vitro study should be specified in the SOP for each test for which the automatic device is employed.

[7] Based on the labeled number of full medication doses, this guidance uses the terms *beginning life stage, middle life stage*, and *end life stage* interchangeably with the terms *beginning of unit life* (the first actuation(s) following the labeled number of priming actuations); *middle of unit life* (the actuation(s) corresponding to 50 percent of the labeled number of full medication doses); and *end of unit life* (the actuation(s) corresponding to the label claim number of full medication doses).

in content uniformity is to be determined based on within and between canister or bottle data, and, for nasal aerosols and suspension formulation nasal sprays, between batch data. Analytical data should be validated,[8] and the analytical validation report should accompany the content uniformity report. For BE data, equivalence of T and R data should be based on the methodology of section IX.A.1.

2. Droplet and Drug Particle Size Distribution (PSD)

To increase nasal deposition and minimize deposition in the lungs and GI tract, aerosol droplets should generally have a mass median aerodynamic diameter (MMAD) greater than 10 to 20 microns (Task Group on Lung Dynamics, 1966). As MMAD decreases over the 5-20 micron range, the Task Group report indicates that reduced nasopharyngeal deposition and increased pulmonary deposition occur. Droplet size distribution measurements are thus critical to delivery of drug to the nose. For BA and BE, studies of droplet size distribution and PSD by validated methods should be performed. For suspension products, drug particle size may be important to rate of dissolution and availability to sites of action within the nose. Therefore, drug or drug and aggregate PSD should be characterized in the formulation both within the can or bottle and within the aerosolized droplets. Present agency experience suggests that drug and drug aggregate PSD characterization cannot be acceptably validated for nasal aerosols and nasal sprays. In this circumstance, drug and drug aggregate PSD studies should be performed, and these supportive characterization data, along with available validation information, should be submitted.

a. Particle size distributions

Droplet Size Distribution

For all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, droplet size distribution should be determined utilizing a method suitable for fully characterizing the droplet size. Laser diffraction methodology, or appropriately validated alternate methodology, is recommended.

Particle Size Distribution

For all nasal aerosols and nasal sprays, whether formulated as solution or suspension products, PSD should be determined using a suitable aerodynamic

[8] A draft guidance for industry is under development on analytical procedures, validation data, and samples for drug substances and drug products.

method (e.g., multistage cascade impactor (CI), multistage liquid impinger (MSLI)).

Drug and Aggregate PSDs

Nasal spray suspension formulations typically contain micronized drug within an aqueous vehicle with partially undissolved suspending agents and other ingredients. Nasal aerosol suspension formulations contain micronized drug suspended within propellants, and may contain a surfactant and/or cosolvent. Light microscopy may be considered for estimating drug and drug aggregate PSD of these products.

b. Instrumental methods

Laser Diffraction

Laser diffraction is a nonaerodynamic optical method of droplet or particle sizing which measures the geometric size of droplets or particles in flight. To characterize the beginning, middle, and end of the plume, measurements should be made at three distances from the delivery orifice. Multiple actuations may be performed at each lifestage to assess precision. The droplet size distributions due to each actuation, and the means, standard deviations (SDs), and percent coefficients variation (CVs) should be reported. At each distance, measurements should be made at different delay times in order to characterize the size distribution of droplets or particles within the plume upon formation, as the plume has started to dissipate, and at some intermediate time (Sciarra and Cutie, 1989). Selected delay times may be based on obscuration levels or other suitable means.[9]

Droplet size distribution data (D_{10}, D_{50}, D_{90}), and span ($(D_{90} - D_{10})/D_{50}$) should be reported based on volume (mass). Droplet size distribution data by count (number of droplets) are not requested. All instrument/computer printouts should be submitted, including cumulative percent undersize tables, histograms of PSD, obscuration values, and other details and statistics. The manufacturer's recommended obscuration ranges for the laser diffraction instrument should be submitted.

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[9] *Obscuration* refers to the percentage of laser light obscured or scattered out of the beam by the sample, and is influenced by sample concentration and width of the plume. Following actuation, obscuration levels are initially low, increase as the plume develops, then decrease as the plume dissipates.

Comparative laser diffraction data are requested at beginning, middle, and end of unit life. For BE, statistical comparisons should be based on D_{50} and span.

Multistage Cascade Impaction (CI) or Multistage Liquid Impinger (MSLI)

Sizing of droplets or particles by CI or MSLI measures aerodynamic diameter based on inertial impaction, an important factor in the deposition of drug in the nasal passages. CI or MSLI data should be provided for all nasal sprays and nasal aerosols to characterize the size distribution of drug based on aerodynamic mass diameters. The greatest percentage of the emitted dose is deposited prior to or on the first stage of the CI for both nasal aerosols and nasal sprays. Thus, equivalence of aerodynamic drug particle size distribution of test and reference products, although conducted by validated procedures, does not ensure equivalent PSD of drug within the aerosolized droplets. Characterization of drug PSD by CI or MSLI, along with the other recommended in vitro tests, does not allow waiver of in vivo BE studies for suspension formulation products (see section II.A).

For BA and BE, CI or MSLI drug deposition profile data should be based on three size range groups. Group 1 includes summation of drug deposition in or on the valve stem, actuator, inlet port, and upper stage, which should have a nominal effective cutoff diameter (ECD) (e.g., greater than or equal to 9.0, 10.0, 13.0, or 16.0 microns). Group 2 includes drug deposition on the stage immediately below the upper stage (e.g., greater than or equal to 5.0 microns). Group 3 includes summation of drug deposition below the Group 2 stage, including the filter. For Group 1 only, deposition should also be reported for each of the individual accessories and the upper stage. Deposition should be reported in mass units. Mass balance accountability (sum of all drug deposited from the valvestem to the filter) should be documented.

Selection of the most suitable cascade impactor may be influenced by the ECDs of stages of various brands of cascade impactors, the geometry of the induction port, and other factors. Studies should use the fewest number of actuations justified by the sensitivity of the analytical method (generally not exceeding 10), in order to be more reflective of the PSD of individual doses. Analytical data should be based on a validated chemical assay. The analytical validation report should accompany the CI data report. The SOP or validation report should indicate the minimum quantifiable amount of drug deposited on each of the three groups of deposition sites and on each accessory or stage of the Group 1 data.

For BA and BE, cascade impactor data are requested at the beginning and end of unit life. Middle of unit life data are not requested. For BE, statistical

comparisons of drug deposition on the three groups should be based on profile analysis (section IX.D).

Light Microscopy

Light microscopy may provide drug and aggregate PSD data. However, the method is limited in its ability to fully characterize PSD by the resolution limit of light mieroscopy (about 0.5 mieron or higher) which may not be adequate for sizing micronized drug. A second limitation is potential difficulty in distinguishing drug from undissolved excipient in suspension formulation nasal sprays. Due to these limitations, acceptable validation of the mieroscopic data may not be possible. In the presence of these limitations, this guidance recommends that comparative drug and aggregate PSD data should be submitted as supportive BA and BE characterization data for suspension formulation nasal aerosols and sprays. The occurrence of drug particles and aggregates within appropriate size ranges should be tabulated for each analysis, and histograms of the drug and aggregate PSD should be provided. Count median diameter (CMD) and geometric standard deviation (GSD) based on single particle data (aggregates excluded) should be provided. Studies of nasal sprays should include test product placebo to provide an estimate of the occurrence of apparent drug particles (*false positives*) due to undissolved excipient. PSD by light microscopy provides supportive BE information.

3. Spray Pattern

Spray pattern characterizes the spray following impaction on an appropriate target (e.g., a thin-layer chromatography (TLC) plate). It provides information about the shape and density of the plume following actuation. Spray patterns should be determined on single actuations at three appropriate distances from the actuator to the target at the beginning and end of unit life. The visualization technique should preferably be specific for the drug substance. End of unit life testing is requested to ensure comparability to performance at beginning of unit life. Clear, legible photographs or photocopies of the spray patterns, not hand-drawn representations obtained by tracing the pattern, should be provided. The widest (D_{max}) and shortest (D_{min}) diameters, and the ovality ratio (D_{max}/D_{min}) should be provided for each spray pattern. The SOP should include a figure describing the procedure for measurement of D_{max} and D_{min}. For BE, statistical comparisons should be based on ovality ratio and either D_{max} or D_{min} data (section IX.B).

Spray pattern and plume geometry (below) are recommended to assist in establishing functional equivalence of products as a result of differences in the device components of T and R products. Comparable spray pattern and plume geometry data for T and R,

combined with other in vitro tests (and in vivo studies for suspensions), ensure equivalent drug deposition patterns, resulting in equivalent delivery of drug to nasal sites of action and equivalent systemic exposure or absorption.

4. Plume Geometry

Plume geometry describes two side views, at 90 degrees to each other (two perpendicular planes) and relative to the axis of the plume, of the aerosol cloud when actuated into space. Plume geometry should be based on high-speed photography or other suitable methods. Photographs should be of high quality and should clearly show the dense cloud and individual large droplets or agglomerates of droplets in the vicinity of the cloud. Plume geometry may be performed only at the beginning of unit life. Plumes should be characterized at three or more times after a single actuation, chosen to characterize the plume early upon formation, as the plume has started to dissipate, and at some intermediate time. Photographs of plumes should be used to measure plume length, plume width, and plume (spray cone) angle. All photographs and data characterizing the plume dimensions in two planes should be submitted, including the scale used to indicate actual size. Comparative BE data are supportive (section IX.C).

5. Priming and Repriming

Priming and repriming data provide information to ensure delivery of the labeled dose of drug, and thus are part of the in vitro BA and BE assessment. Similar studies should be conducted on nasal sprays. For products approved under an NDA, priming and repriming data based on single actuations should be provided for multiple orientations.

For products approved under an ANDA, the labeling is the same as that for the reference listed drug, except for specific changes described in the regulations (21 CFR 314.94(a)(8)(iv). For nasal sprays and some nasal aerosols, the reference product labeling (package insert and/or patient package insert) describes the number of actuations necessary to prime the product on initial use and on repriming following one or more periods of nonuse (e.g., 24 hours and 7 days following last dose). Comparative priming and repriming data are requested to document that priming of the test product is attained within the number of priming actuations stated in the reference product labeling. For reference product nasal aerosols lacking priming recommendations, priming studies are recommended to characterize the test product relative to the reference product. In the absence of reference product priming recommendations, an adequate number of single actuations should be studied to ensure that test and reference products have each attained an emitted dose equal to the labeling claim. Repriming studies of test products are requested only when the reference product labeling includes repriming instructions.

Priming and repriming data for the test product in multiple orientations should be provided in the CMC portion of the ANDA submission. Therefore, comparative BE studies may be based on products stored in the valve upright position. For any nasal aerosol product in which the reference product labeling recommends storage in the valve down position, additional comparative priming and repriming data should be provided for this orientation. For suspension products, the unprimed canister or bottle should be shaken for a standardized time (e.g., 5 seconds) and a dose should then be immediately collected. For nasal aerosols, a standardized period (e.g., 30-60 seconds) should be allowed between successive actuations. Doses may be collected in the same apparatus used for the dose or spray content uniformity through container life test. When priming and/or repriming information is included in the labeling, comparison of equivalence should be based on the emitted dose of the single actuation immediately following the specified number of priming or repriming actuations (section IX.B). The emitted dose of each earlier actuation should also be provided. When priming information is not specified, the emitted dose of each successive actuation up to and including attainment of label claim should be provided. Comparative BE data in the absence of priming are supportive (section IX.C).

6. Tail Off Profile

Whereas dose or spray content uniformity conducted at the end of the labeled number of actuations ensures that the product delivers the labeled dose through the number of actuations stated in product labeling, the tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations (i.e., from end of unit life to product exhaustion). Tail off profile characteristics may vary as a function of valve or pump design, bottle geometry, and other factors, and may be characterized in terms of uniformity of decline, rate of decline, and intercanister or interbottle variability in unit dose (Schultz, 1995). For BA assessment, tail off data are noncomparative. For BE assessment, comparative tail off profiles are requested to ensure similarity in drug delivery as the product nears exhaustion. Data should be based on the emitted dose of individual actuations. Comparative BE data are supportive; however, the test product should be no more erratic in dose delivery than the reference product, and the rate of decline in delivery should be generally similar between products.

VI. BIOAVAILABILITY AND BIOEQUIVALENCE: CLINICAL STUDIES FOR LOCAL DELIVERY

A. GENERAL INFORMATION

The same adequate and well-controlled clinical trials in humans used to establish the safety and effectiveness of the drug product (21 CFR 314.126) may be used, in some cases, to establish BA

or, when comparative, BE (21 CFR 320.24). Although BA and BE studies with a clinical endpoint are sometimes incapable of showing a dose-response relationship and may not be consistently reproducible (21 CFR 320.24(b)(4)), they are sometimes the only means available to document BA and BE in drug products intended for local delivery and action. A number of FDA guidances provide information about the general conduct of clinical studies, including clinical studies to document BA and BE. These include: *General Considerations for Clinical Trials* (International Conference on Harmonisation (ICH) E8, December 1997); *Structure and Content of Clinical Study Reports* (ICH E3, July 1996); *Good Clinical Practice: Consolidated Guideline* (ICH E6, May 1997); and *Statistical Principles for Clinical Trials* (ICH E9, May 1997).

B. BE CLINICAL STUDY ENDPOINTS

Clinical evaluations should be made at baseline and during treatment. The efficacy endpoint should be patient self-rated total nasal symptom scores (TNSS). These most often include a composite score of runny nose, sneezing, nasal itching, and for drugs other than antihistamines, congestion. The efficacy endpoint should be expressed as change from baseline (pretreatment) of the TNSS, expressed in absolute units and percent change. In addition to the efficacy measures, all three study designs should incorporate safety assessments.

C. CLINICAL STUDY BATCHES

The product quality BA batch used for the study should be the same pivotal clinical trial batch used in the in vitro BA studies (section V.A). Where BE studies are needed for an NDA, the batches of test and reference products should be the same batches employed in the in vitro testing. The product quality batches used to establish the local delivery BE for an ANDA should be the test and reference batches employed in the in vitro BE testing.

D. CLINICAL BE STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA

A BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should document sensitivity of the study to discriminate between differing doses (i.e., show a dose-response relationship). This documentation typically relies on the inclusion of a second dose of the reference product, and preferably of the test product, that may be higher or lower, to demonstrate that the efficacy response is different between the two doses. Doses may differ by two or fourfold, and to increase study sensitivity, the lower dose examined may be below the minimum labeled dose (e.g., one-half or one-quarter of the recommended dose, depending on the limitations of the formulation).

Although many clinical study design options may be considered to establish BE, outlined below are three suggested study designs for evaluating clinical responses for nasally administered drugs for seasonal allergic rhinitis (SAR): (1) traditional treatment, (2) day(s) in the park, and (3)

environmental exposure unit (EEU). The three study designs use SAR patients as the study population to document BE for all indications in product labeling for nasally administered drug products covered in this guidance. Recommended studies are designed as treatment studies rather than prophylaxis studies. Depending on the time to onset of therapeutic effect of the drug being tested, the medication effect can be evaluated after a single dose (e.g., antihistamines) or after short-term treatment (e.g., corticosteroids). In all three study designs, an assessment of onset of action and efficacy at the end of the dosing interval is recommended, because both measures are important clinically and may offer better dose discrimination.

Because specific study recommendations are not provided in this guidance, a protocol for a BE study with a clinical endpoint for a specific suspension drug product should be submitted to the appropriate review division at FDA.[10] For the three study designs, a pilot study may be useful to determine the optimal dosing duration and doses to be used in the BE study.

1. Traditional Treatment Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study with a single-blind placebo lead-in period (generally 1 to 14 days) in which efficacy and safety of the test product are assessed for a 2-week duration. Symptom assessment should be made at least twice daily (i.e., *reflective* scores) and also at the end-of-dosing interval (i.e., *instantaneous* scores). Evaluation of both reflective and instantaneous assessments of the total nasal symptom score are critical in establishing BE with a clinical endpoint. Safety measures should include physical examination, laboratory monitoring (chemistry, liver function tests, hematology, urinalysis, serum pregnancy testing in females), monitoring of vital signs, adverse event reporting, and performance of 12 lead ECGs before and after treatment with study drug.

2. Day(s) in the Park Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study in a park setting in which subjects are exposed to relevant outdoor allergens. On the study day, patients should undergo a baseline period of evaluation in the park setting to establish a minimum level of allergic rhinitis symptoms prior to randomization to study drug treatment. Patients should remain outdoors in the park for a prespecified length of time over one to two consecutive days. Nasal symptoms should be evaluated on a periodic basis throughout the full dosing interval to characterize onset of action and end-of-dosing interval efficacy. Safety assessment generally involves adverse event reporting.

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[10] A draft guidance on clinical development programs for allergic rhinitis drug therapy is under development.

3. Environmental Exposure Unit (EEU) Study

The recommended design for this study is a randomized, double-blind, placebo-controlled, parallel group study in a controlled indoor environment termed an *EEU chamber*. Repeated pretreatment exposure to the relevant allergen allows screening for symptomatic responders for enrollment in the treatment phase. On the study day, patients should be exposed to the allergen in the EEU and monitored for a baseline period to ensure a minimum level of allergic rhinitis symptoms prior to randomization to study drug treatment. Patients should remain in the EEU for a prespecified length of time over one or two days. Nasal symptoms should be evaluated on a periodic basis throughout the full dosing interval to characterize onset of action and end-of-dosing interval efficacy. Safety assessment generally involves adverse event reporting.

Subjects employed in each of the three study designs should be patients with a history of SAR, and a positive allergy test for specific allergens (e.g., allergen skin test). Patients with other significant diseases should be excluded from the study. Patients should be experiencing a defined minimum level of symptom severity at the time of study enrollment.

VII. BIOAVAILABILITY AND BIOEQUIVALENCE: PK SYSTEMIC EXPOSURE STUDIES

Plasma concentration-time profiles from BA and BE studies should be used to evaluate systemic exposure for suspension drug products that produce sufficiently high drug concentrations of the active ingredient and/or active moiety after nasal administration to obtain meaningful AUC and C_{max} data. The product quality BA study to characterize systemic exposure may be one of the same PK studies conducted to address clinical pharmacology and biopharmaceutics questions of regulatory interest. The BA study may be conducted in healthy subjects or SAR patients. The BA batch used for the PK systemic exposure study preferably should be a pivotal clinical trial batch. Alternatively, a PK batch similar to a batch used in a pivotal clinical trial may be used, in which case, any differences between the PK batch and the pivotal clinical trial batch should be discussed with appropriate CDER review staff prior to the study. If the PK batch is not one of the three batches used for the in vitro BA studies (section V.A.1), in vitro BA data should be provided for the PK batch using the same protocols as for the three batches.

For an NDA or an ANDA, the in vivo BE study should be conducted with a replicate crossover or nonreplicate crossover design. The study may be single or multiple dose. The batches of test and reference product should be batches employed in the in vitro testing. For an ANDA, the batches of test and reference used for the systemic exposure study should be the same batches used for the clinical study for local delivery, and each of these batches should be one of the three batches used for the in vitro BE studies. Subjects for the study should be healthy (non-SAR

patients), with exclusions primarily for reasons of safety. Several actuations from the drug product in each nostril may be needed to achieve measurable concentrations of the active ingredient and/or active moiety in an accessible biological fluid such as blood or plasma. For an ANDA, an IND in accordance with 21 CFR 320.31 will be needed when the number of doses in a single-dose or multiple-dose study exceed the single or total daily dose specified in the labeling of the approved NDA.

Attempts should be made in the conduct of a PK systemic exposure study to minimize loss of drug due to excess fluid drainage into the nasopharynx or externally from the nasal cavity. The bioanalytical method should be validated for accuracy, precision, specificity and sensitivity. Statistical analysis should be conducted on the log-transformed data. Average BE may be used for studies with replicate crossover or nonreplicate crossover designs. Individual BE with scaling may be used for studies with replicate crossover designs. A pilot study is recommended to assess the analytical methodology and to estimate the numbers of actuations and subjects to be used in the full-scale study.

VIII. BIOAVAILABILITY AND BIOEQUIVALENCE: PHARMACODYNAMIC OR CLINICAL STUDIES FOR SYSTEMIC ABSORPTION

A. GENERAL INFORMATION

Clinical studies for BA, or BE studies with a pharmacodynamic or clinical endpoint, are needed to assess the systemic absorption of those suspension drug products for which PK systemic exposure studies (Section VII) are not feasible. Published data suggest that systemic BE of suspension formulation antihistamine nasal products may be established based on PK data (Heykants et al., 1995). At the present time, approved nasal mast-cell stabilizer nasal spray and anticholinergic nasal spray products are solutions for which BE may be established based upon in vitro studies only. These types of studies will thus generally be needed only for corticosteroid nasal aerosols and nasal sprays. The product quality BA study to characterize systemic absorption may be one of the same clinical studies conducted to establish the safety of the active ingredient and/or active moiety in the drug product. Because this section does not provide specific recommendations for clinical studies for systemic absorption, sponsors should submit a protocol for a BE study with a pharmacodynamic or clinical endpoint for a specific drug product to the appropriate review division at FDA.

B. BE STUDY ENDPOINTS FOR CORTICOSTEROIDS

The recommended systemic absorption BE study design for nasal corticosteroids is suppression of the HPA axis. The endpoint may be either 24-hour urinary free cortisol adjusted for urinary creatinine, based on a full 24-hour urine collection, or serum cortisol levels collected every 4

hours over a 24-hour period, with exclusion of the middle of the night sample. Endpoints for placebo and test and reference treatments should be baseline-adjusted prior to statistical analyses.

C. CLINICAL STUDY BATCHES

The product quality BA batch used for the study should be a pivotal clinical trial batch used in the in vitro BA studies (section V.A). For BE studies for an NDA, the batches of T and R should be batches used in in vitro testing. For an ANDA, the batches of test and reference product used for the systemic absorption study should be the same batches used for the clinical study for local delivery. Each of these batches should be one of the three batches used for the in vitro BE studies.

D. CLINICAL STUDY DESIGNS AND SUBJECT INCLUSION CRITERIA

The study can be conducted as a placebo-controlled, randomized, multiple-dose parallel design comparing test and reference products. The study should be conducted in healthy, nonallergic volunteers not previously exposed to corticosteroids, and subjects should be domiciled within the clinical study center during the dosing days. Three treatments, test and reference products at the labeled dose (maximum labeled dose when labeling includes more than one dose) and a placebo of the test product, should be used. Each treatment period should consist of 14 days of dosing. Timed urine or serum samples for determination of 24-hour urinary free cortisol or 24-hour serum cortisol levels should be collected prior to dosing (baseline) and during the last 24-hours of the 14 days of dosing. In addition, we recommend determining two to three interval 24-hour urinary free cortisol or 24-hour serum cortisol levels (e.g., performing additional assessments on days 4, 7, and/or 10) to better profile the onset of the effect of test and reference products, should detectable adrenal suppression occur.

Alternatively, the study could be conducted as a placebo-controlled, randomized, multiple-dose crossover design comparing test and reference (Wilson et al., 1998). As in the parallel design study, the study should be conducted in healthy, non-allergic volunteers not previously exposed to cortocosteroids. During the dosing days, subjects should be domiciled within the clinical study center to ensure compliance with the study protocol. Three treatments, test and reference at the labeled dose (maximum labeled dose when labeling includes more than one dose), and a placebo of the test product should be used. Each treatment period should consist of 14 days of dosing. A shorter dosing duration would be considered with adequate scientific justification. Washout periods between treatments should be adequate to eliminate the possibility of a carryover effect. Urine or serum samples for determination of 24-hour urinary free cortisol or 24-hour serum cortisol levels should be collected prior to each dosing period (baseline data) and during the last 24-hours of each dosing period. In addition, we recommend determining two to three interval 24-hour urinary free cortisol or 24-hour serum cortisol levels (e.g., performing additional assessments on days 4, 7, and/or 10) to better profile the onset of the effect of test and reference products,

should detectable adrenal suppression occur.

IX. STATISTICAL ANALYSES

In vitro studies yield both profile and nonprofile data, which require different statistical analyses. Noncomparative BA in vitro data analyses for both profile and nonprofile data are discussed in section IX.A. For BE studies, methods of comparison for nonprofile analyses are discussed in section IX.B, for supportive nonprofile and profile analyses in section IX.C, and for profile analyses in section IX.D. Methods for comparison of categorical endpoints from the SAR studies are discussed in section IX.E.

A. IN VITRO BA DATA

Means, SDs, and percent CVs should be reported for the measures recommended in this guidance to document BA.

μ_T	=	T means (log scale)
σ_{BT}	=	T between batch standard deviations (log scale)
σ_{CT}	=	T between canister standard deviations (log scale)
σ_{LT}	=	T within canister between life stage standard deviation

The overall means for the formulation should be averaged over all bottles or canisters, life stages (except for priming and repriming evaluations), and batches. In addition to overall means, means at each lifestage for each batch averaged over all bottles or canisters, and for each lifestage averaged over all batches, are requested. For profile data, means, SDs, and percent CVs should be reported for deposition in each of Groups 1, 2 and 3 of the CI or MSLI data, as well as on the individual accessories and stage within Group 1.

B. IN VITRO BE DATA: NONPROFILE ANALYSES USING A CONFIDENCE INTERVAL APPROACH

Nonprofile analyses should be applied to the following tests: (1) dose or spray content uniformity through container life; (2) droplet size distribution; (3) spray pattern; and (4) priming and/or repriming, when this information is specified in the labeling.

1. Study Protocol

Data for the BE criterion should be based on testing a suitable number of bottles or canisters from each of three batches of the T and R drug products. Each bottle or canister should be tested for the measure (parameter) of interest at beginning and end, or

beginning, middle, and end of unit life, as indicated in section V and Table 1. Rather than evaluate performance at each life stage separately, a criterion is recommended that combines the multiple life stages. In doing so, the multiple life stages are considered as providing measures of the same underlying quantity. The recommended criterion considers deviations from uniformity across bottle or canister life stages; results are ideally uniform. Lack of uniformity between life stages should be treated as another variance component in the criterion.

For suspension formulation nasal sprays and solution formulation and suspension formulation nasal aerosols, the number of canisters or bottles (units) of product to be studied should not be fewer than 30 for each of the test and reference products (i.e., no fewer than 10 from each of three batches). For solution formulation nasal sprays, no fewer than 10 units from each of the three batches or three sublots should be studied. The number of units is a function of T to R product means and variances. Estimates of these mean differences and variances will necessitate pilot studies.

2. Criterion for Comparisons, Confidence Interval, and Bioequivalence Limit

The equivalence approach for nonprofile tests relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit for the criterion.

a. Criterion for comparison

The in vitro population BE criterion and BE limit are:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_R^2} \leq \theta$$

where:

μ_T, μ_R	=	T and R means (log scale)
σ_{BT}, σ_{BR}	=	between batch T and R standard deviations (log scale)
σ_{CT}, σ_{CR}	=	between canister T and R standard deviations (log scale)
σ^2_R	=	$\sigma^2_{BR} + \sigma^2_{CR} + \sigma^2_{LR}$
σ^2_T	=	$\sigma^2_{BT} + \sigma^2_{CT} + \sigma^2_{LT}$
σ_{LT}, σ_{LR}	=	within T and R canister between life stage standard deviation
θ	=	in vitro BE (upper) limit

The overall means for the two formulations should be averaged over all bottles or canisters, life stages (except for priming and repriming evaluations), and batches.

The general approach should be to calculate a 95 percent upper bound for the criterion. If this upper bound is less than or equal to the upper limit, θ, the test product may be judged to be bioequivalent to the reference product at the 5 percent level. The criterion will be further discussed in the guidance for industry on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (draft December 1997), when finalized. A population, rather than average, bioequivalence criterion is recommended in order to estimate whether the test product may be more variable than the reference product. The test product should be as or more consistent in the delivery of drug than is the reference product. An individual BE approach is not appropriate for in vitro data because there are no subjects, thus no subject-by-formulation interaction.

b. Determining a 95 percent upper bound

CDER recommends that a method of moments approach be used for estimating the means and variances needed to determine the population bioequivalence criterion. Approaches based on restricted maximum likelihood (REML) may be used in special cases. For determining the 95 percent upper bound, CDER recommends using a method analogous to one proposed for individual bioequivalence (Hyslop, Hsuan and Holder 1998).

c. Specification of the population BE upper limit

The general form of the upper limit, θ, is analogous to the form of the population BE criterion, which is

$$\frac{(\text{mean difference in natural log scale})^2 + \text{variance terms}}{\text{comparison variance}}$$

The corresponding form for the upper limit is then

$$\frac{(\text{average BE limit in natural log scale})^2 + \text{variance terms offset}}{\text{scaling variance}}$$

This formula contains three values to be specified: (1) average BE limit, (2) variance terms offset, (3) and scaling variance. These values will be specified when this guidance is finalized based on simulation work now in progress.

Average BE Limit

Due to the low variability of in vitro measurements, at the present time CDER recommends that the limit not be be larger than 90/111 (i.e., the ratio of geometric means would fall within 0.90 and 1.11). A value of 0.90 is tentatively recommended as the average BE limit. This value should be used in calculating the population BE limit (refer to θ in the equation in section IX.B.2.a, above).

Variance Terms Offset

This value arises to allow some difference among the total variances that may be inconsequential. In this regard, the variance terms offset is analogous to the average BE limit. The variance terms offset also helps correct for the effect on power and sample size for the need to estimate the variances. Because of the low variability of in vitro measurements, the variance terms offset, denoted ϵ_p in the draft guidance on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (December 1997), when finalized, should be taken as 0.0. CDER is also considering ϵ_p equal to 0.01.

Scaling Variance

This value adjusts the BE criterion depending on the reference product variance. When this variance is greater than the scaling variance, σ_{T0}^2, the limit is widened. When this variance is less than the scaling variance, the limit is narrowed.

Mixed scaling should be employed for in vitro studies, as described in the draft guidance on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (December 1997), when finalized. With mixed scaling, when the reference variance ***in the study*** is less than the scaling variance, the population BE criterion should be modified to its *constant-scaled* form:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\sigma_{T0}^2}$$

Mixed scaling is used to avoid penalizing test products for cases with very low reference variance. It is CDER's current intent to select σ_{T0} for in vitro studies so that most studies will use constant scaling and thus, that σ_{T0} will be at least 0.10.

The upper limit may be interpreted by reference to a population distance ratio (PDR). The PDR is the ratio of the test-reference distance (in the log scale) to the reference-reference distance. In contrast to individual BE, the distances for population BE are based on administration to separate individuals (further details will be provided in the guidance for industry on *In Vivo Bioequivalence Studies Based on Population and Individual Bioequivalence Approaches* (draft December 1997), when finalized. The population BE criterion, denoted by PBC, is related to the PDR by

$$PDR = (1 + \frac{PBC}{2})^{\frac{1}{2}}$$

Substituting the BE limit θ for PBC expresses the upper limit in the PDR scale. The specification of 0.90 for the average limit, 0.0 for the variance offset, and 0.10 for the scaling standard deviation corresponds to an upper limit for PDR of 1.25.

C. IN VITRO BE DATA: SUPPORTIVE NONPROFILE AND PROFILE ANALYSES

The following tests provide supportive characterization data: (1) plume geometry; (2) tail off profile; (3) priming data, when reference product labeling does not specify priming information; and (4) drug CMD and drug and aggregate PSD data from microscopic analyses. The comparative data requested in section V should be provided, based upon the same number of bottles or canisters recommended in the protocol of section IX.A.1. Statistical criteria need not be applied.

D. IN VITRO BE DATA: PROFILE ANALYSES USING A CONFIDENCE INTERVAL APPROACH

Profile analyses apply to cascade impactor (CI) or multistage liquid impinger (MSLI) data for nasal aerosols and nasal sprays. Analyses may rely on a criterion for comparisons of means and variances relative to a BE limit, with calculation of a 90 percent confidence interval. The general approach is adaptable to cascade impactors of varying numbers of stages and accessories, or groups of stages and accessories. As discussed in section V.B.2, profile comparisons may be based on drug deposition within three groups.

1. Study Protocol

Data for the BE criterion should be based on testing a suitable number of bottles or

canisters from each of three batches of the T and R drug products (or three sublots for solution formulation nasal sprays). Each canister should be tested for deposition at the beginning and end life stages, as indicated in section V.B.2. The number of canisters to be studied from each batch, which should not be less than 10, is a function of test to reference product means and variances. Estimates of these mean differences and variances will require pilot studies.

2. Criterion for Comparison

The criterion considered appropriate for the profile comparison is:

$Rd \leq \theta$

where:

Rd	=	in vitro BE criterion
θ	=	in vitro BE limit

Rd is derived with the following notation:

Let:

P_R, P_T	=	population mean profile across the batches of the reference product and test product
F_{BR}, F_{BT}	=	distribution of deviation of batch mean from population mean profile of the reference product and test product
F_{CR}, F_{CT}	=	distribution of deviation of canister mean from batch mean profile of reference product and test product
p_R, p_T	=	observed profile of a given puff of reference product and test product (i.e., p_R has a compound distribution of MN(100, P_R), F_{BR} and F_{CR}, and p_T has a compound distribution of MN(100, P_T), F_{BT} , and F_{CT}, where MN(100, P) is a multinomial distribution with n=100 and P=(p_1, p_2, …, p_S) for an impactor of S stages)

and:

d_{TR}	=	observed distance between p_R and p_T, the test-reference distance
$d_{RR'}$	=	observed distance between p_R and $p_{R'}$, the reference-

		reference distance (i.e., reference-reference deviation)
rd	=	$d_{TR}/d_{RR'}$, observed ratio of test-reference distance to reference-reference deviation

The in vitro BE measure is defined by

Rd = E(rd)

where:

E(rd)	=	expected value of rd

Further information on d_{TR}, $d_{RR'}$, rd, and the in vitro profile comparison procedure is provided in Appendix A.

3. Determining a 95 Percent Upper Bound

Since there is no exact or asymptotic distribution of the average rd, the 95% upper bound should be determined by the 95th percentile of the empirical sampling distribution generated by a random sample of the matched triplet (test, reference 1, reference 2) of canisters. A description of the procedure is provided in Appendix B.

4. Specification of the Upper Limit

Reserved (simulation studies to develop specifications for the upper limit are ongoing).

E. IN VIVO BE DATA: CATEGORICAL ENDPOINTS

Reserved (statistical analyses are under development).

X. MULTIPLE STRENGTHS

A small number of nasal sprays for local action are available in two strengths. Current examples are: (1) ipratropium bromide nasal spray, a solution formulation; and (2) beclomethasone dipropionate nasal spray, a suspension formulation. Lower strengths of a product ordinarily would achieve the lower dose per actuation using a lower concentration formulation, without changing the actuator and metering valve or pump (other than diptube) used in the higher strength product. The following sections describe recommended BA and BE studies for low strengths of nasal sprays for which BA or BE for the higher strengths has previously been established.

Recommendations are also provided for cases in which BA or BE is initially established on the low-strength product. No approved nasal aerosols are available in multiple strengths, thus BA and BE recommendations are not considered for these products.

A. SOLUTION FORMULATION NASAL SPRAYS

BA of lower or higher strength solution formulation nasal sprays should be based on conduct of all applicable in vitro tests described in section V. These studies are generally noncomparative in character. Documentation of BE between T and R products should follow the recommendations described in section III regarding formulation and container and closure system. Abbreviated in vitro testing (section V) is recommended to document BE of the low-strength T product to the low-strength R product, provided BE of the high-strength product has been documented.

In vitro test	High Strength	Low Strength
Dose content uniformity	BE[1]	BE
Priming and repriming	Yes	Yes
Tail off	Yes	Yes
Droplet size distribution		
By laser diffraction	BME	B
By cascade impactor	BE	No
Spray pattern	BE	B
Plume geometry	B	No

[1] Beginning (B), Middle (M), End (E)

With the exception of the reduced testing, the same protocols and acceptance criteria used to establish BE of the high strength products should be used for the low strength products. In vivo studies are not needed for documentation of BA or BE of solution formulation nasal sprays. For cases in which BE is documented for the low-strength product, to subsequently document BE for the high-strength product, all applicable in vitro tests described in section V should be conducted.

B. SUSPENSION FORMULATION NASAL SPRAYS

BA of lower strength suspension formulation nasal sprays should be based on conduct of all applicable in vitro tests described in section V and systemic exposure studies, assuming availability of bioanalytical methodology to allow measurement of systemic concentrations. In the absence of this methodology, BA for systemic absorption should be documented through clinical studies. BE conditions for the lower strength product should be the following:

1. Documentation of BE for the high-strength test products and high-strength reference

products, based on acceptable comparative formulations and container and closure systems, comparative in vitro data, and comparative in vivo data

2. Acceptable comparative formulations and container and closure systems for the low-strength test products and low-strength reference products

3. Acceptable comparative studies for low-strength test products and low-strength reference products for all applicable in vitro tests in section V

4. Proportionally similar unit dose between high- and low-dose test product and high- and low-dose reference product

5. Equivalent droplet and drug PSD between high- and low-dose test product and high- and low-dose reference product

Provided the above conditions are met, in vivo studies are not needed for documentation of BE of the lower strength products.

For cases in which an ANDA applicant initially documents BE on the low-strength product, and subsequently submits an ANDA for the high-strength product, full in vitro and in vivo documentation of BE should be provided for the high-strength product. For cases in which an ANDA applicant has documented BE for its high-strength product and wishes to conduct applicable in vitro tests and in vivo study on the low-strength product, BE criteria need not include in vitro comparisons between high- and low-strength products.

XI. SMALLER CONTAINER SIZES

Nasal aerosols and nasal sprays may be available in two container sizes. Current examples are: (1) beclomethasone dipropionate nasal aerosol, a suspension formulation; (2) fluticasone propionate nasal spray, a suspension formulation; and (3) cromolyn sodium nasal spray, a solution formulation. Smaller container sizes of nasal aerosols should be formulated with the same components and composition, metering valve, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Smaller container sizes of nasal sprays should be formulated with the same components and composition, pump, and actuator as the large container size that was studied in pivotal clinical trials (NDA) or for which BE has been documented (ANDA). Where this is the case, no further documentation of either BA or BE is necessary. However, reestablishing proper priming, given a change in the dead volume of the pump and actuator, may in some cases be appropriate (see section V.B.5).

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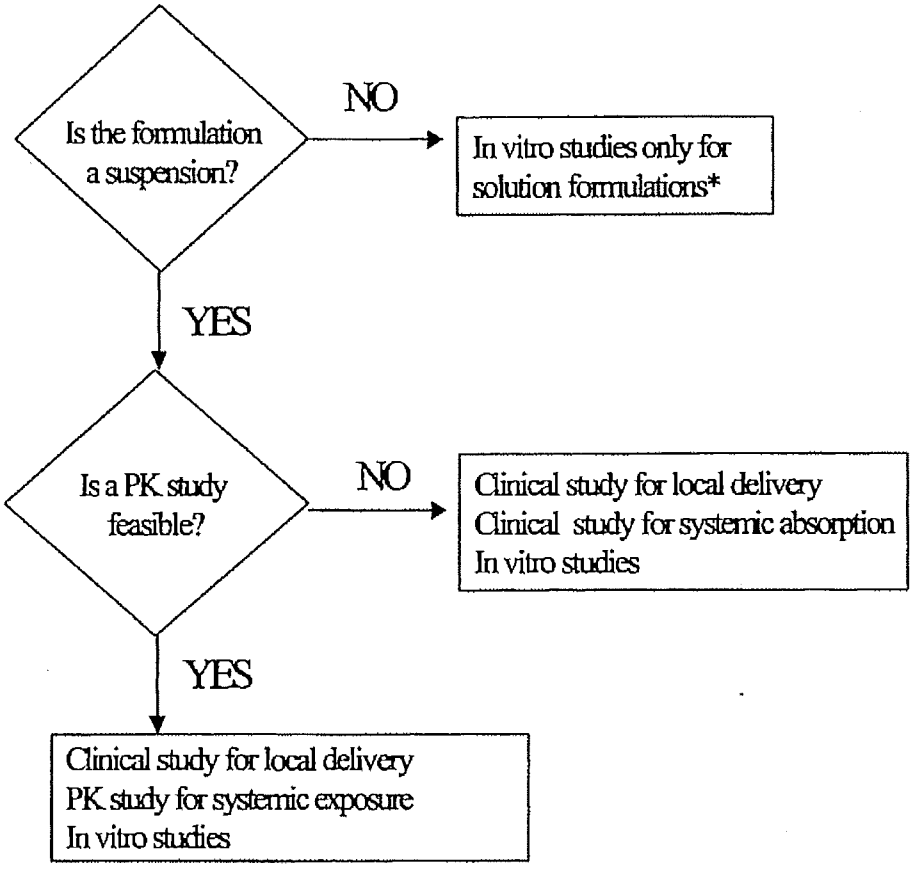
Decision Tree For Product Quality
BA and BE Studies For Nasal Aerosols and Nasal Sprays



*See Section II (A) regarding additional in vivo BA studies needed for solution and suspension formulations.

Table 1
In Vitro BA and BE Studies for Nasal Aerosols and Nasal Sprays

TEST	BA AND BE STUDY MEASURE(S)[1]	BE MEASURES[2]	LIFESTAGE(S) B (beginning) M (middle) E (end)	CONFIDENCE INTERVAL OR SUPPORTIVE CHARACTERIZATION FOR BE	GUIDANCE SECTIONS
Dose or spray content uniformity through container life	Drug mass per single dose	Same as previous column	B, M, E (aerosols) B, E (sprays)	Confidence interval	V.B.1, IX.B
Droplet size distribution	D_{10}, D_{50}, D_{90}, span	D_{50}, span	B, M, E	Confidence intervals	V.B.2, IX.B
Particle size distribution (CI or MSLI)	Deposition profile over 3 groups	Same as previous column	B, E	Confidence interval	V.B.2, IX.D
Drug and aggregate PSD of suspensions (light microscopy)	Drug CMD and GSD; aggregate PSD	Drug CMD	B	Supportive characterization	V.B.2, IX.C
Spray pattern	D_{max}, D_{min}, ovality ratio	D_{max} or D_{min}, ovality ratio	B, E	Confidence intervals	V.B.3, IX.B
Plume geometry	Length, width, spray cone angle (if feasible)	Same as previous column	B	Supportive characterization	VB.4, IX.C
Priming and repriming	Drug mass per single actuation	Same as previous column for: • priming, and • repriming if in precursor product (R) labeling	From first actuation (priming); from first actuation after specified period of nonuse (repriming)	Confidence interval for priming and repriming if in precursor product (R) labeling; supportive characterization of priming when not in labeling	V.B.5, IX.B, IX.C
Tail off	Drug mass per single actuation	Same as previous column	From end of labeled number of actuations to exhaustion	Supportive characterization	V.B.6, IX.C

[1] Data requested as part of the BA or BE submission.
[2] Measures requested for comparative in vitro BE documentation.

APPENDIX A
IN VITRO PROFILE COMPARISON PROCEDURE BASED ON CHI-SQUARE DIFFERENCES

This appendix describes a method of comparing cascade impactor (CI) or multistage liquid impinger (MSLI) deposition profiles on "S" stages or accessories, or groups of stages and accessories, from droplet and/or particle sizing studies. Equivalence may be assessed by comparing the profile difference between test product and reference product canisters (nasal aerosols) or bottles (nasal sprays) to the profile variation between reference product canisters or bottles. The profile comparison is based on chi-square differences.

The following table represents the population mean profiles P_T and P_R of one test canister and one reference canister, respectively.

Product	Stage										
	1	2	3	4	.	.	s	.	.	S	Total
Test	P_{T1}	P_{T2}	P_{T3}	P_{T4}	.	.	P_{Ts}	.	.	P_{TS}	100
Reference	P_{R1}	P_{R2}	P_{R3}	P_{R4}	.	.	P_{Rs}	.	.	P_{RS}	100

The profile difference between test and reference product canisters is assessed by the chi-square measure as follows:

$$D_{TR} = (P_{T1} - P_{R1})^2/((P_{T1} + P_{R1})/2) + (P_{T2} - P_{R2})^2/((P_{T2} + P_{R2})/2) + \ \ldots \ +$$

$$(P_{TS} - P_{RS})^2/((P_{TS} + P_{RS})/2)$$

Similarly, the profile variation (i.e., difference) between any two canisters of the reference product is:

$$D_{RR'} = (P_{R1} - P_{R'1})^2/((P_{R1} + P_{R'1})/2) + (P_{R2} - P_{R'2})^2/((P_{R2} + P_{R'2})/2) + \ \ldots \ +$$

$$(P_{RS} - P_{R'S})^2/((P_{RS} + P_{R'S})/2)$$

The approach involves a comparison of D_{TR}, the profile difference between one test canister and one reference canister, to $D_{RR'}$, the profile variation between two canisters of the reference product, where the latter is based on two randomly selected reference canisters. The comparison of profile differences is given by the ratio of D_{TR} to $D_{RR'}$. A large D_{TR} is one that is large relative to the variation that would be expected between two canisters of the reference product.

In order to estimate D_{TR} and $D_{RR'}$, the observed data of one canister of test product and two different canisters of reference product need to be matched as a triplet. The observed profiles of the three canisters of a given triplet may be represented in the following table.

Product	Stage										
	1	2	3	4	.	.	s	.	.	S	Total
Test	p_{T1}	p_{T2}	p_{T3}	p_{T4}	.	.	p_{Ts}	.	.	p_{TS}	100
Reference 1	p_{R1}	p_{R2}	p_{R3}	p_{R4}	.	.	p_{Rs}	.	.	p_{RS}	100
Reference 2	$p_{R'1}$	$p_{R'2}$	$p_{R'3}$	$p_{R'4}$	.	.	$p_{R's}$	.	.	$p_{R'S}$	100

The observed profile difference d_{TR} between test and reference products is:

$$d_{TR} = (p_{T1} - (p_{R1} + p_{R'1})/2)^2/((p_{T1} + (p_{R1} + p_{R'1})/2)/2) + (p_{T2} - (p_{R2} + p_{R'2})/2)^2/((p_{T2} + (p_{R2} + p_{R'2})/2)/2)$$

$$+ \ \ldots \ + (p_{TS} - (p_{RS} + p_{R'S})/2)^2/((p_{TS} + (p_{RS} + p_{R'S})/2)/2).$$

The reference product canister-to-canister variation within the triplet is estimated by the profile difference between the two paired reference canisters, R and R':

$$d_{RR'} = (p_{R1} - p_{R'1})^2/((p_{R1} + p_{R'1})/2) + (p_{R2} - p_{R'2})^2/((p_{R2} + p_{R'2})/2) + \ \ldots \ + (p_{RS} - p_{R'S})^2/((p_{RS} + p_{R'S})/2).$$

For a given triplet of canisters (Test, Reference 1, Reference 2), the ratio of d_{TR} to $d_{RR'}$ may be obtained as follows:

$$rd = d_{TR}/d_{RR'}.$$

Assuming that there are N(T, R, R') triplets in the sample, the unbiased estimate of Rd [=E(rd)] is the sample mean of the N observed $d_{TR}/d_{RR'}$ values.

For an experiment consisting of three lots each of test and reference products, and with 10 canisters per lot, the lots can be matched into six different combinations of triplets with two different reference lots in each triplet. The 10 canisters of a test lot can be paired with the 10 canisters of each of the two reference lots in $(10 \text{ factorial})^2 = (3{,}628{,}800)^2$ combinations in each of the lot-triplets. Hence a random sample of the N canister-pairing of the six Test-Reference 1-Reference 2 lot-triplets is needed. Rd is estimated by the sample mean of the rd's calculated for the triplets in the selected sample of N:

$\hat{}Rd$ = sample mean of $(d_{TR}/d_{RR'})$.

APPENDIX B

DETERMINATION OF THE 95% UPPER BOUND FOR IN VITRO PROFILE COMPARISONS

Assume the profile comparison is to be carried out with a random sample with no replacement of N = 500 matches (from the population of 6 x (10 factorial)^2 matches). The average of the 500 sample rd's (= d_{TR} /d_{RR}) gives ^Rd. The 95% upper bound of Rd is the 95th percentile of the 500 calculated rd's (i.e., the 25th largest rd among the 500 calculated rd's).

EXHIBITS 5 -7
REDACTED
IN ITS ENTIRETY